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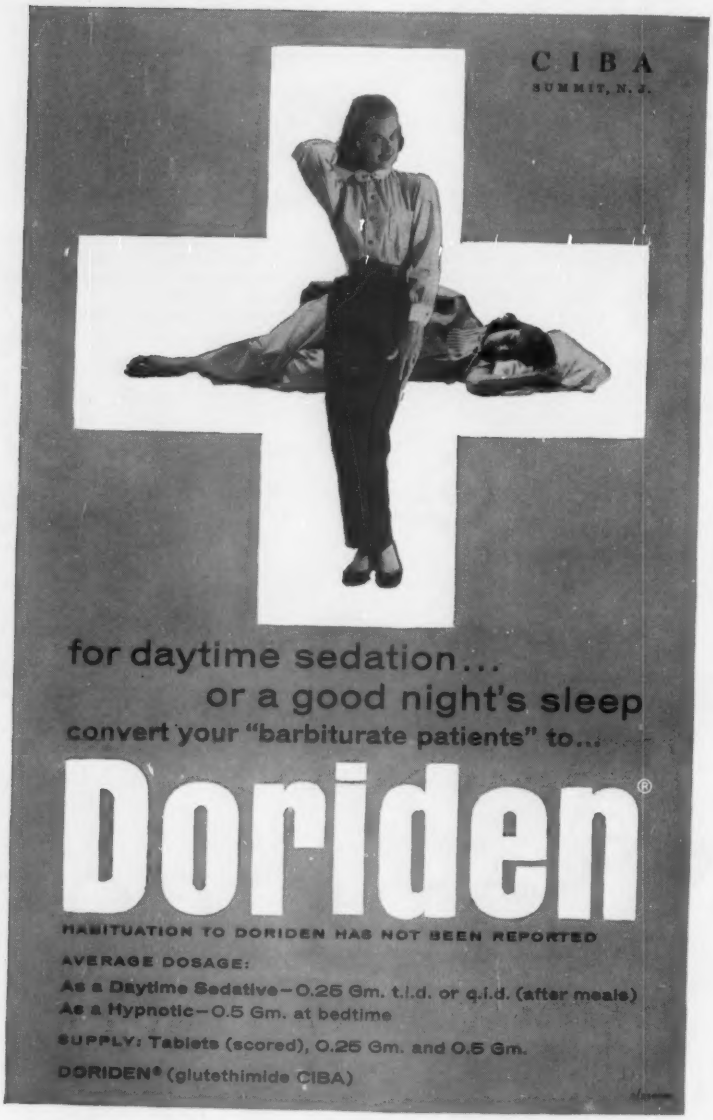
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REFERENCE: 1. Robinson, R. C. V., *J.A.M.A.* 157:1300, April 9, 1955.

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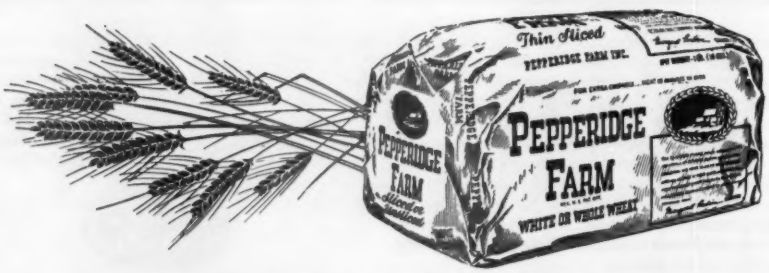

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*Riese, J. A.: Am. J. Digest. Dis. *21*:81, 1954.

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In undernourished subjects the maintenance requirement for each essential amino acid is much greater—two to almost five times greater—than in healthy subjects.

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B complex vitamins also affect the metabolism of proteins and amino acids. For example, rats fed a high protein diet require a high intake of B complex vitamins in order to maintain normal growth rates. Omission from the ration of any one of these vitamins (riboflavin, thiamine, pyridoxine, or pantothenate) is accompanied, in varying degrees, by lower food consumption and slower weight gain.

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*Cannon, P. R.; Frazier, L. E., and Hughes, R. H.: Factors Influencing Amino Acid Utilization in Tissue Protein Synthesis, in Symposium on Protein Metabolism, New York, The National Vitamin Foundation, Inc., 1954, pp. 55-90.

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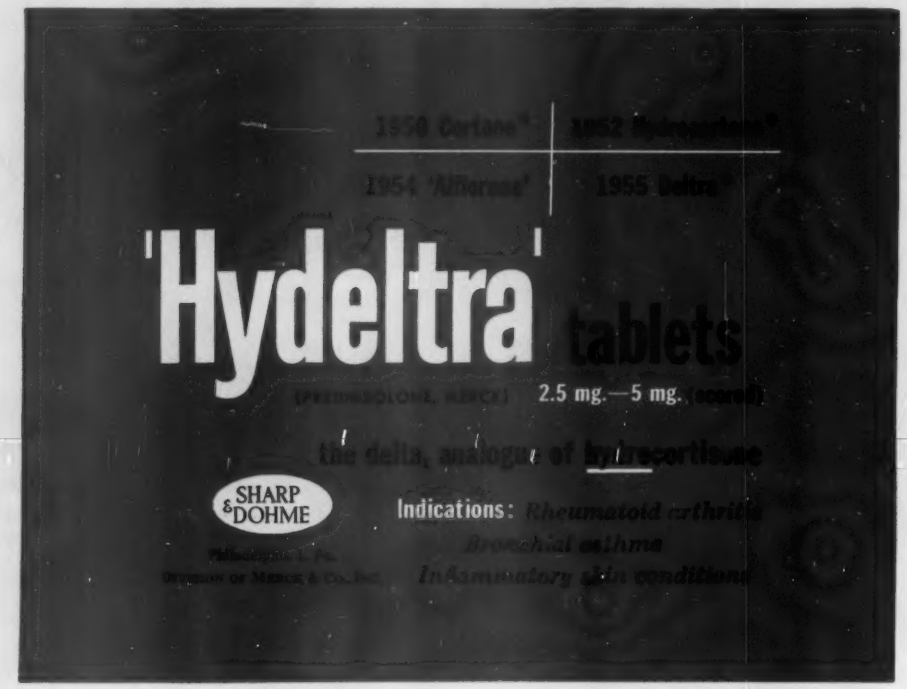

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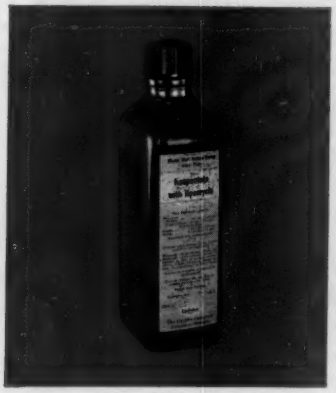

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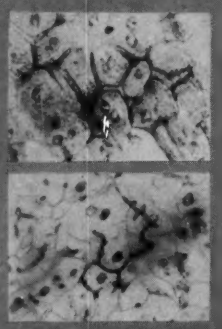

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(1) Clara, M.: Med. Monatsschr. *7*:356, 1953. (2) Brauer, R. W., and Pessotti, R. L.: Science *115*:142, 1952. (3) Schwimmer, D.; Boyd, L. J., and Rubin, S. H.: Bull. New York M. Coll. *16*:102, 1953.

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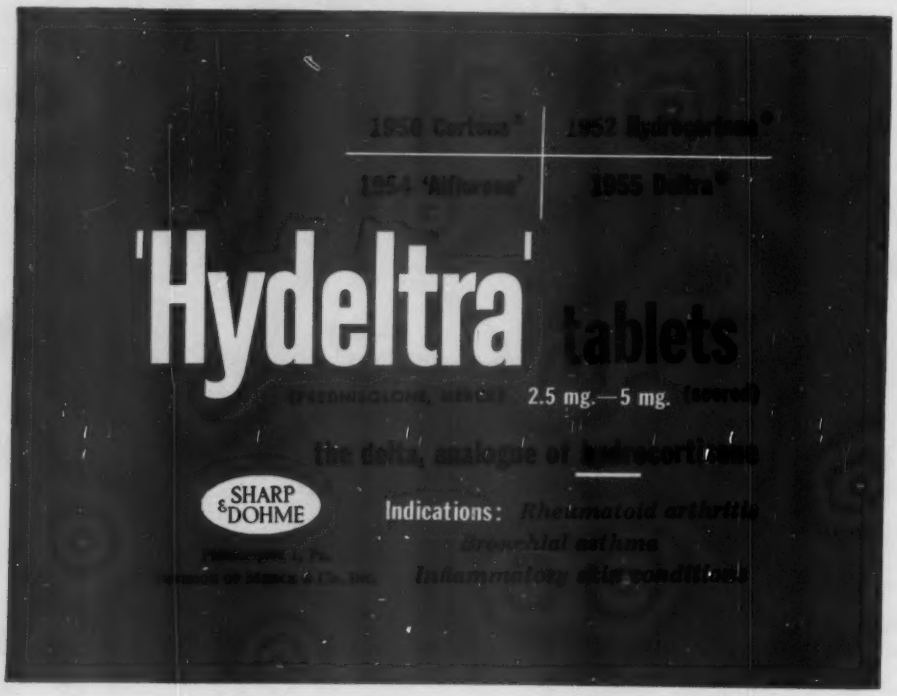
1. Piper, C. E., and Nicklas, F. W.: Indust. Med. 23:510, 1954.



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1. Science News Letter, March 1954
2. Greenblatt, R. B.: Obstet. & Gyn. 2:530, 1953

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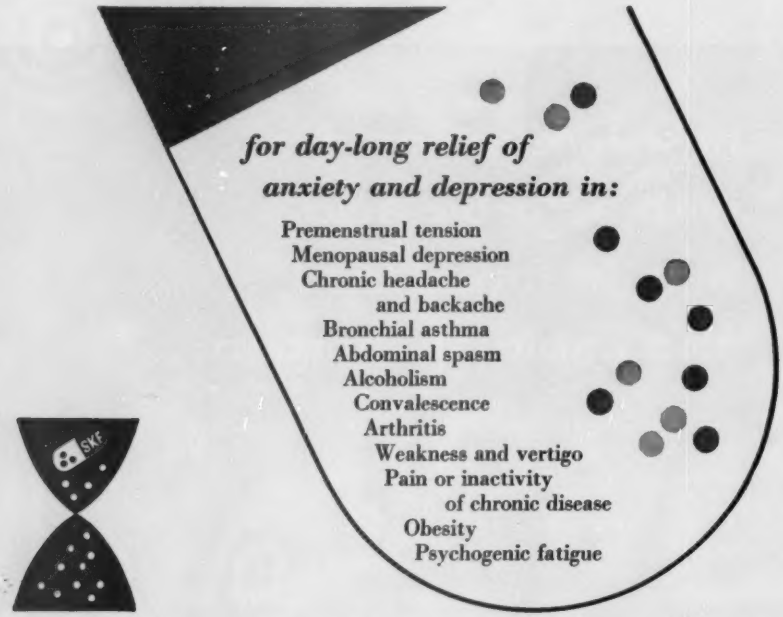

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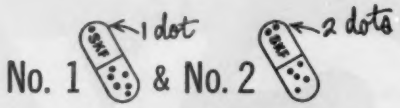

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1. Chamberlain, D.T.: Gastroent. 17:224-5, 1951. 2. McHardy, G., and Browne, D.C.: South. M.J. 45:1139, 1952. 3. Pakula, S. F.: Postgrad. Med. 11:123, 1952.

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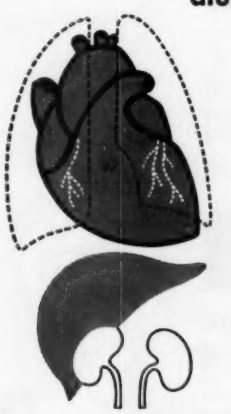

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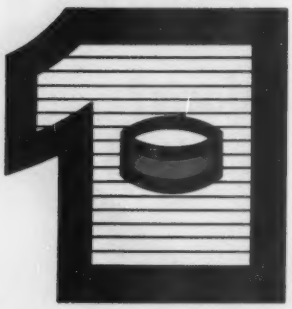

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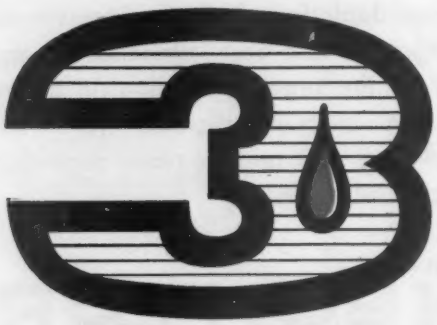

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DRUG THERAPY IN HYPERTENSION WITH HEMORRHAGIC HYPERTENSIVE RETINITIS*

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THE purpose of this paper is to add our experience with the newer hypotensive drugs in the treatment of patients with severe hypertension and hemorrhagic eye grounds to the ever-growing list of reports on this subject. This treatment is too new to justify any final conclusions, but, in our short experience, it does appear to offer more than any previous medical therapy in this devastating disease.

Since hypertension can be a benign disease with no effect on longevity, or a rapidly progressing, fatal disease, it is difficut to evaluate the effects of therapy on the final outcome. Keith, Wagener and Barker[1] have shown, however, that the prognosis in untreated patients with hemorrhagic eye grounds is invariably poor (Fig. 1). It is for this reason that we have selected patients with Grades 3 and 4 hypertension, as classified by Keith, Wagener and Barker, for reporting the results of drug therapy.

To exclude the patients in the terminal stages of this disease who are placed on therapy as a last desperate attempt to postpone catastrophe, we have not included in this series patients treated for less than four months.

Before therapy was begun all the patients were carefully studied to rule out curable causes of hypertension such as pheochromocytoma, coarctation of the aorta, Cushing's disease, renal disease and certain brain tumors. In addition all patients had the following studies: 7-foot chest roentgenogram for heart size, electrocardiogram, cold-pressor test, determination of phenolsulfonphthalein excretion, urea clearance and nonprotein nitrogen, concentration test, urinalysis and complete blood counts. An intravenous pyelogram was obtained in most cases. During the period of this study 79 patients with Grades 3 and 4 hypertension were subject to splanchnicectomy, some of the better risks thus being removed from this series.

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Patients selected for treatment with the potent drugs were first placed on *Rauwolfia serpentina* (Raudixin), 50 to 100 mg. three times daily, or reserpine (Serpasil), 0.1 to 0.25 mg. three times daily, for three to six weeks at home. An increase in complaints of unpleasant nasal congestion was noted with the higher dosage schedule. After this period of "priming" with *R. serpentina* the patients were hospitalized, and usually one of the autonomic blocking agents were added. Previously, we used hexamethonium by injection or orally, but since the advent of pentolinium (Ansolysen) we have all but abandoned hexamethonium because of the alleged more prolonged and predictable effect of pentolinium.

By "priming" the patients with *R. serpentina* before starting the ganglionic blocking agents we have been able to use smaller doses of the blocking agents with fewer side actions and smoother blood-pressure curves. None of these 78 patients with severe Grade 3 or 4 hypertension showed adequate response of blood pressure to this "priming" period on *R. serpentina*.

When we first began using the ganglion-blocking agents *R. serpentina* was not available, and hydralazine hydrochloride (Apresoline) was given in conjunction with hexamethonium, beginning with 25 mg. two to four times daily and gradually increasing the dose until satisfactory lowering of the blood pressure was obtained. Recent experience with hydralazine, however, indicates that in large dosage (400 mg. or more daily) it has certain toxic effects such as bone-marrow depression, a rheumatoid type of arthritis and a syndrome resembling acute systemic lupus erythematosus. These effects will be reported in a separate communication. We believe that the threat of these toxic effects, although infrequent and usually relieved by discontinuance of the drug, tends to outweigh the beneficial effects, especially when the blood pressure can be controlled with less toxic drugs. The fact that this treatment is directed toward control of the hypertension rather than cure and therefore must be continued for the life of the patient me-

diates against the use of a potentially toxic drug when it is not absolutely necessary. If hydralazine is used, the daily dose probably should not exceed 200 mg. Thus far, administration of hexamethonium or pentolinium has not resulted in any toxic effects other than too vigorous blocking of the autonomic ganglions from overdosage.

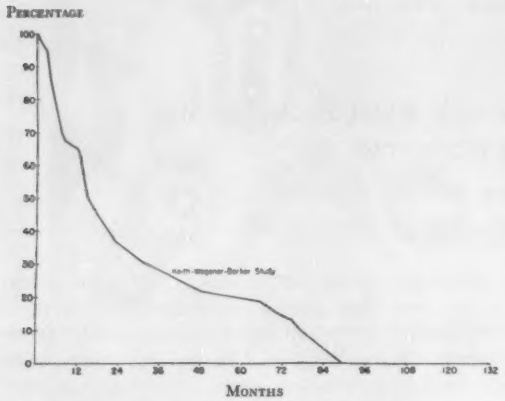

FIGURE 1. *Cumulative Survival Curve for Patients with Grade 3 Hypertension (Based on Keith, Wagener and Barker[1]).*

When *R. serpentina* became available and was added to the regimen of patients already taking hexamethonium, it was soon noted that in three to six weeks patients were experiencing hypotensive reactions and the dose of hexamethonium could be substantially reduced (Fig. 2).

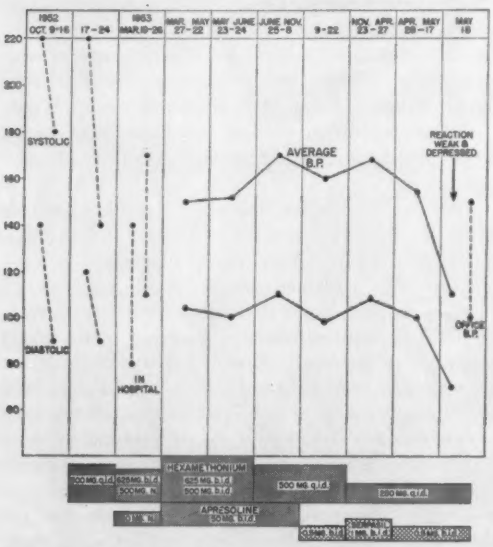

FIGURE 2. *Fall in Blood Pressure with Reserpine (Serpasil).*

Adjustment of the dose of hexamethonium and pentolinium was sometimes troublesome, but could usually be accomplished satisfactorily. Treatment was not always pressed to the point of bringing the systolic pressure down to 120 mm. of mercury, as recommended by Smirk,[2] but was often tapered off at the dose necessary to keep the pressure below 170 systolic, 100 diastolic. Our over-all long-term goal is to keep patients living at a diastolic pressure between 90 and 110 mm. of mercury when they are in the standing position. With diastolic pressures at these figures, regardless of systolic pressures, the degenerative signs of renocardiovascular disease usually subsided, and symptoms were controlled. Hexamethonium is started in doses of 125 mg. orally or 20 mg. subcutaneously four times a day. The oral dose is increased 125 mg. if the systolic blood pressure taken while the patient is standing, just before the scheduled dose is given, is over 150 mm. of mercury; if the pressure is 130 mm. or less, the dose is decreased by 125 mg. Hypotensive reactions at any time call for a reduction in the dose of hexamethonium. Parenteral therapy is adjusted similarly, but in 5-mg. amounts. If the patient fails to have a bowel movement for three consecutive days a laxative or enema is advised, and oral administration of hexamethonium is discontinued until a bowel movement occurs. This was necessitated by the fact that hexamethonium is usually incompletely absorbed during its travel through the intestinal tract, but constipation prolongs its stay in the intestinal tract, resulting in increased absorption. Since pentolinium, with its more predictable intestinal absorption, became available it has

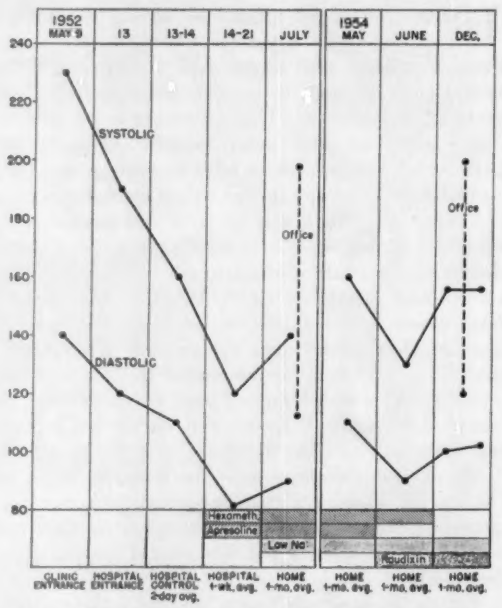

FIGURE 3. *Typical Graph of Blood-Pressure Readings in the Hospital, at Home and in the Office.*

been possible to control the pressure more adequately without the danger of serious hypotensive reactions. This therapy is begun with 10 mg. four times daily before meals and at bedtime, and the dosage is increased or decreased by 10 mg. according to the schedule described above.

While in the hospital, patients are taught to take their own blood pressures and to plot them on graph paper. The pressure is recorded before the drug is taken and one hour and three hours afterward to determine the time of maximal drug effect. Pressures are taken with the patient in the standing position to record the lowest drop in pressure. The graph reveals the "trend" of the blood pressure. Usually, the patient can be discharged in twelve to fourteen days; he has his own sphygmomanometer and stethoscope and continues to record his blood pressure at home. For several weeks after discharge it is necessary tc follow the patients closely and keep adjusting the dose of drug to compensate for tolerance. Once the dose is stabilized, the interval between visits can be extended considerably.

TABLE 1. *Results of Medical Treatment in Hypertensive Patients Followed for Four to Thirty-One Months after the Beginning of Treatment.*

HYPERTENSIVE MANIFESTATION	PATIENTS IMPROVED	PATIENTS SAME	PATIENTS WORSE	PATIENTS WITH UNKNOWN RESULT
Grade 3 hypertension — 56 patients:				
Blood pressure	53	2	1	0
Fundi	34	14	1	7
Kidneys	5	5	8	38
Grade 4 hypertension — 22 patients:				
Blood pressure	16	1	5	0
Fundi	17	5	0	0
Kidneys	4	2	3	13

The necessity for keeping blood-pressure records at home is demonstrated in Figure 3. In this case the high blood-pressure reading obtained on a revisit to the clinic apparently indicated that the treatment had had no effect. Since all the patients had two days of hospital observation before ganglion-blocking agents (or, in some cases, hydralazine) were added to the "priming" course of *R. serpentina* we have included a control period to show that the blood-pressure records at home actually averaged lower. Thus, the effects of the drugs could be measured not only against the high, psychically stimulated levels obtained in the physician's office but also against the control levels while the patient was at hospital rest.

For patients who cannot take their own blood pressures Smirk[2] has suggested the "standing test." Patients are advised to stand absolutely still for one minute at the time of maximal drug action; they should note a slightly hypotensive reaction if they are taking sufficient medication. We have had little experience with this method, but Smirk reported very favorably on it.

RESULTS OF TREATMENT

Grade 3 Hypertension

Fifty-six patients with Grade 3 hypertension were treated for four to thirty-one months. Of this group 53 had a significant drop in blood pressure (Table 1), and 34 showed improvement in the fundi, with absorption of hemorrhages and exudates.

Splanchnicectomy and sympathectomy had previously been performed on 10 of these patients. It was noted that they responded to smaller doses of hexamethonium and pentolinium than would have been expected if operation had not been performed. One of this group died.

Forty-two of the original 56 patients are alive.

TABLE 2. *Cause of Death in Patients with Grades 3 and 4 Hypertension Treated Medically.*

CAUSE OF DEATH	PATIENTS WITH GRADE 3 DISEASE	PATIENTS WITH GRADE 4 DISEASE
Cerebrovascular accident	4	2
Uremia	4	3
Other (related to hypertension)	2	3
Unknown	4	1
Totals	14	9

Grade 4 Hypertension

Twenty-two patients with Grade 4 hypertension were treated, and 16 showed a significant drop in blood pressure. Eight patients had an elevated nonprotein nitrogen value or other evidence of severe renal impairment before treatment was instituted. Of these 22 patients 13 survive.

TABLE 3. *Four-Month to Thirty-One-Month Survival in 78 Patients with Grades 3 and 4 Hypertension Who Had Drug Therapy.*

TOTAL CASES	PATIENTS WITH NO FOLLOW-UP STUDY	PATIENTS WHO SURVIVED	IMPROVEMENT IN BLOOD PRESSURE
			%
Patients with Grade 3 disease:			
56	5	41(80.4%)	94.6
Patients with Grade 4 disease:			
22	1	14(66.6%)	46.0

The principal cause of death was uremia, with cerebrovascular accidents a close second. Myocardial infarction, congestive heart failure and hypertensive encephalopathy accounted for the remainder.

Both Groups

The results of treatment are summarized in Table 1, and the causes of death are listed in Table 2.

Table 3 records the survival figures of the 78 patients in this study. Of the patients with Grade 3 hypertension 80.4 per cent survived for four to thirty-one months although almost all (94.6 per cent) had a significant drop in blood pressure.

Of the patients with Grade 4 hypertension 66.6 per cent survived a similar period of observation and treatment, although only 46 per cent of this very severely ill group had a significant drop in blood pressure.

Summary and Conclusions

Seventy-eight patients with hemorrhagic hypertensive retinitis (Grades 3 and 4 hypertension) were treated with combinations of the newer hypotensive agents, 55, or 70.5 per cent, of the 72 patients who were followed surviving from four to thirty-one months. Seventeen of the series had evidence of severe renal involvement before treatment was started. Although it is too early to evaluate survival rates in this group the results are encouraging.

The drugs, themselves, are not without danger unless the dose is carefully controlled. One can best accomplish this by beginning treatment in the hospital and teaching patients to take and record the blood pressure at home.

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RESULTS OF SPLANCHNICECTOMY ON PATIENTS WITH HEMORRHAGIC HYPERTENSIVE RETINITIS*

Ione Huntington, M.D.,† and James A. Evans, M.D.‡

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WE have chosen the classification in the title merely for its simplicity and because the patients who most need salvage because of their poor prognosis are those with Grades 3 and 4 hypertension.

This report is a study of the survival rate of patients who underwent splanchnicectomy during the period from 1935 through 1949, all of whom had hemorrhagic eye grounds and a few of whom had areas of prehemorrhagic capillary dilatation. These were cases of Grade 3 or 4 hypertension according to the classification of Keith, Wagener and Barker.[1]

Many other authors have reported increased survival rates with sympathectomy over those obtained by medical treatment. Smithwick and Thompson[2] found the mortality in Grade 3 hypertension, (as classified by them) to be 71 per cent after five years when medical treatment and only 20 per cent when surgical treatment was given. In cases of Grade 4 hypertension, the mortality at five years was 90 per cent for those treated medically and 59 per cent for those treated surgically. This corroborated and extended work that Smithwick[3] had described earlier.

Peet,[4] and Woods and Peet,[5] with a less extensive surgical procedure (bilateral subdiaphragmatic splanchnicectomy), reported a lower mortality after operation. They classified hypertension differently, but in cases corresponding to our Grade 4, the mortality one year after surgery was 36 per cent (78 per cent expected with medical treatment)[1]; two years after surgery it was 50 per cent (88 per cent expected with medical treatment), and after five years 35 per cent of patients were still living.

Bechgaard[6] and Hammarström and Bechgaard[7] also noted an increased survival rate in patients who had had sympathectomy. In their group with Grade 4 hypertension, at five years the survival rate of patients treated surgically was 50 per cent, and that of those treated medically was 14 per cent. Again, the patients with Grade 3 hypertension were classified differently from ours.

Craig,[8] Morrisey et al.[9] and Evans and Bartels[10] and many others have also reported an increased survival rate after sympathectomy.

Method

Of a total of 206 cases reviewed it was impossible to obtain a recent follow-up report in 17, leaving 189 cases with a follow-up period of four to nineteen years. The first operation was performed nineteen years ago. One patient, a woman with Grade 4 hypertension, is alive fourteen and a half years after operation; this represents the longest survival. Most of the patients had their follow-up examinations at the clinic; in other cases information was obtained by letters from the patient, his relatives, or his physician. Of the 189 patients 147 had Grade 3, and 42 had Grade 4 hypertension. Of the former 73 were males, and 74 females; of the latter 28 were males, and 14 females.

Most of the patients had the extensive dorsolumbar sympathectomy (fourth thoracic to the second lumbar ganglion) as previously described by Poppen and Lemmon,[11] but the 12 patients surviving for more

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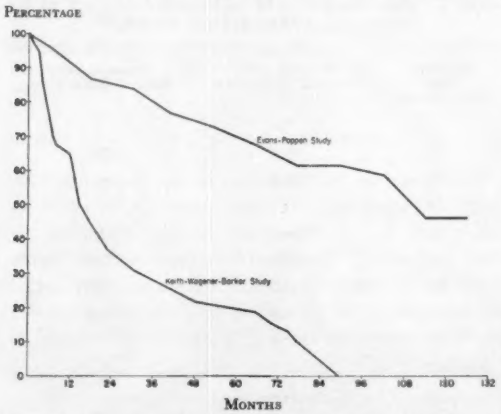
than four years who were operated on before 1942 had a more limited procedure, consisting of resection of the tenth or twelfth thoracic to the second or third lumbar ganglion, with resection of the greater and lesser splanchnic nerves and celiac ganglion. In many patients sympathectomy was the only specific therapy. Some have been placed on low-sodium diets, and recently 6 have been given hexamethonium and hydralazine (Apresoline), 4 *Rauwolfia serpentina* and hydralazine, and 1 *R. serpentina,* hexamethonium and hydralazine. The survival curves (Fig. 1 and 2) are estimated to ten and a half years only because there were not enough patients in the group operated on ten and a half to nineteen years ago to be statistically reliable.

Survival Rate in Grade 3 Hypertension

The longest-surviving patient among those with Grade 3 hypertension was a man operated on at the age of forty-four who died twelve and a half years after operation.

Of the 147 patients with Grade 3 hypertension who were operated on, 3 died after operation, an operative mortality of 2.0 per cent. Of the 144 patients who survived the operation 90 (62.5 per cent) lived or are still living four to fourteen and a half years after operation. Fifty-five patients died during a thirteen-year interval.



The Evans–Poppen study was completed by Huntington and Evans at the time this paper was written.

FIGURE 1. *Survival of Patients with Grade 3 Hypertension Treated Surgically Compared with Those Treated Medically (Based on Keith et al.[1] and Huntington and Evans).*

The cumulative rate compounds each year's survivals, after admission to the study, using the group for which complete information is available for the year. Some of the deaths over a long period were not due to hypertension, since some mortality is expected in any population — especially persons of chronic-disease age.

The cumulative survival curve according to age is shown in Figure 1 and Table 1. After four and a half years of follow-up study the cumulative survival was 72.8 per cent compared with an expected cumulative survival of 22 per cent reported by Keith et al.[1] At five and a half years, survival was 67.3 per cent, against an expected figure of 20 per cent. Of the patients operated on six and a half years previously, 61.9 per cent survived, as compared with an expected survival of 10 per cent. Among those operated on eight and a half years previously the survival rate was 56.2 per cent (against none for the series of Keith, Wagener and Barker[1]), and among those followed for ten and a half years, the rate was 46 per cent, against none expected. Criteria for selection compared closely with those of Keith, Wagener and Barker[1]; hemorrhagic eye grounds without papilledema was required for classification as Grade 3 hypertension. Both groups also corresponded closely in age, sex and race.

TABLE 1. *Cumulative Survival Rates for Patients with Grade 3 Hypertension.*

Month after Classification	Survival after Surgical Treatment*	Survival after Medical Treatment†
	%	%
6	95.9	74
18	87.1	47
30	83.7	32
42	76.2	25
54	72.8	22
66	67.3	20
78	61.9	10
90	61.9	0
102	56.2	
114	46.0	
126	46.0	

*Data of Huntington & Evans.
†Data of Keith et al.[1]

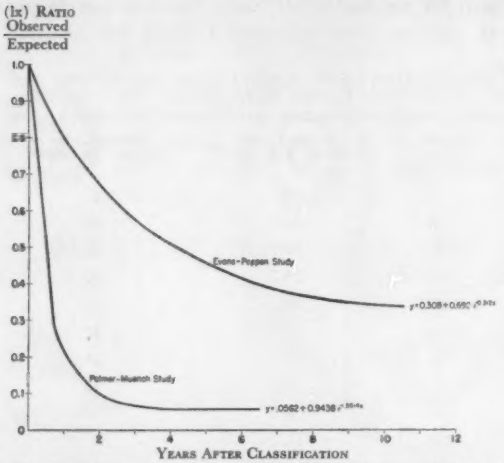
Survival Rates in Grade 4 Hypertension

The patient with Grade 4 hypertension who survived the longest was a woman operated on at the age of thirty-four who is still living fourteen and a half years later. Among the 42 patients with Grade 4 hypertension there were 3 postoperative deaths, an operative mortality of 7.1 per cent.

Because Palmer and Muench[12] figured their control series of medically treated patients with Grade 4 hypertension according to a relative survival curve in a normal (life-table) group of the same age and sex composition as ours, we subjected our survival curve to the same statistical treatment for comparative purposes — the so-called lx ratio (Fig. 2 and Table 2).* The lx ratio was 47.8 per cent compared with a 5.7 per cent expected rate at four and a half

*Our groups were submitted to different statistical disciplines to correspond to the treatment by Keith et al.[1] of their control group for Grade 3 and to that of Palmer and Muench[12] for Grade 4. During the period of this study so many of our patients with severe hypertension accepted operation that we did not have an adequate number of patients with Grade 3 or 4 hypertension to make up our own control series.

years, was 43.2 per cent compared with an expected rate of 5.6 per cent at five and a half years, and 39.9 per cent compared with an expected rate of 5.6 per cent at six and a half years.* At eight and a half years the lx ratio was 35.6 per cent, and at ten and a half years, it was 33.4 per cent. It must be realized, however, that all patients with Grade 4 were not accepted for operation since we demanded no irreversible azotemia disease and no congestive heart failure as criteria for sympathectomy and the control series cited presumably included such desperate, often moribund, patients. However, since almost all of both the good and the poor risks making up the medically treated series of Palmer and Muench[12] (treated by diet, rest, sedatives and nitrites) were dead at four and a half years, it is obvious that the surgically treated patients have a greater chance for survival.



The Evans–Poppen study was completed by Huntington and Evans at the time this paper was written.

FIGURE 2. *Survival of Patients with Grade 4 Hypertension Treated Surgically Compared with Those Treated Medically (Based on Palmer and Muench[12] and Huntington and Evans).*

The "relative survival" rate refers to the survival ratio experienced, compared with that expected in a life-table population. Therefore, it measures the added risk of the condition to the mortality that would be found in a general population group of the same age, sex and race composition. This can be further classified into a group with ultimately expected "normal" mortalities, which may be considered a "cured" proportion. The remainder die at a rate in excess of "normal" — the degree of this rate measures the extra risk imposed on the "uncured" fraction. In patients with Grade 4 disease the "cured" proportion was 0.056 and the risk rate 1.55 in the series of Palmer and Muench[12] and 0.308 and 0.31, respectively, in that of Huntington and Evans.

Cause of Death in Grades 3 and 4 Hypertension

At the time of last follow-up examination 26 of the 42 patients with Grade 4 and 58 of the 147 with Grade 3 hypertension were dead. This gives a total of 84 deaths out of 189 patients up to fourteen and a half years after operation. Six deaths occurred postoperatively, and 2 deaths were totally unrelated to the hypertension. Four others were only indirectly related: 1 patient died of gastrointestinal bleeding (questionably uremic); 1 died while receiving electric-shock therapy; 1 died of a pulmonary embolus secondary to congestive heart failure; and the fourth died in shock after a later operation for a bleeding peptic ulcer.

Of the remaining 72 deaths cardiac disease accounted for 8, cerebrovascular accidents for 20, and uremia for 10. The cause of death was not ascertained in 34 patients.

Status of Surviving Patients with Grade 3 Hypertension

Of the 89 patients with Grade 3 hypertension still living four to twelve and a half years after operation, 66 felt well. Five of these are on hexamethonium and hydralazine, 4 on *R. serpentina* and hydralazine, and 1 on hexamethonium, hydralazine and *R. serpentina*. In 60 patients, or 67 per cent, the blood pressure fell to a satisfactory level (Table 3); in 28 patients, or 31 per cent, it either was maintained or returned to hypertensive levels, but many of these patients were relieved of their previous symptoms and felt well.

TABLE 2. *Ratio of Observed to Expected Survival of Patients with Grade 4 Hypertension.**

Month after Classification	Survival after Surgical Treatment†	Survival after Medical Treatment‡
	%	%
6	90.0	49.1
18	74.1	14.9
30	62.5	7.5
42	54.0	6.0
54	47.8	5.7
66	43.2	5.6
78	39.9	5.6
90	37.5	
102	35.7	
114	34.4	
126	33.4	

*lx ratio changed to percentage.
†Data of Huntington & Evans.
‡Data of Palmer & Muench.[12]

In 54 of the 89 patients the ocular fundi no longer showed any hemorrhagic retinitis. At the last follow-up examination, 9 had hemorrhages in the fundi. In 30 there was an improvement in cardiac function and heart size or electrocardiographic findings, or both. Twenty-six patients manifested little change in cardiac status, and 12 experienced a definite increase

*The lx ratio is changed to percentages actually for the purpose of comparison in Table 2. The difference between the percentages in Table 2 and the lx figures in the curve (Fig. 3) consists in multiplication of the latter by 100.

in cardiac disease — often in the form of myocardial infarction or congestive heart failure. In the majority of patients there was no marked change in kidney function although many showed a decrease in albuminuria and nocturia. In 4, kidney function definitely improved as shown by test, whereas in 6 it became worse — in most cases evidenced by a rise of nonprotein nitrogen level over 40 mg. per 100 cc. Twelve of these 89 living patients had nonfatal cerebrovascular accidents postoperatively.

Status of Surviving Patients with Grade 4 Hypertension

Of the 16 patients with Grade 4 hypertension still living four to fourteen and a half years after operation, 12 felt well. One of these is now on hydralazine, and 1 on hexamethonium and hydralazine. Thirteen of these patients, or 81 per cent, obtained a satisfactory fall in blood pressure (Table 4). In 3 patients hypertension continued or recurred, but the patients experienced relief of symptoms. Twelve patients also showed disappearance of the hemorrhagic retinitis and papilledema. The fundal status is unknown in 4. Cardiac function and heart size or electrocardiogram, or both, revealed improvement in 5 and little change in 7. Four patients experienced an increase in cardiac symptoms. Kidney function definitely improved in 4 patients and deteriorated in 3. In 8 patients there was little change except for decreased nocturia and albuminuria in some. The renal status is unknown in 1 case. Of these 16 living patients, 1 had a nonfatal cerebrovascular accident after the operation.

Table 3. *Results of Sympathectomy in 89 Patients with Grade 3 Hypertension Still Living Four to Twelve and a Half Years after Operation.*

Hypertensive Manifestation	Patients Improved	Patients Unchanged	Patients Worse	Patients with Unknown Result
Blood pressure	60	28	0	1
Fundi	54	9	1	25
Heart	30	26	12	21
Kidneys	4	52*	6	27

*Many had practically normal renal studies before operation.

Observation on Cerebrovascular Accidents after Splanchnicectomy

Since 13 nonfatal and 20 fatal cerebrovascular accidents (18 per cent) have occurred in both groups several months to years after operation in the 183 surviving patients, we are impressed by the fact that splanchnicectomy does not reverse cerebral atheromatous disease.

Table 4. *Results of Sympathectomy in 16 Patients with Grade 4 Hypertension Still Living Four to Fourteen and a Half Years after Operation.*

Hypertensive Manifestation	Patients Improved	Patients Unchanged	Patients Worse	Patients with Unknown Result
Blood pressure	13	3	0	0
Fundi	12	0	0	4
Heart	5	7	4	0
Kidneys	4	8*	3	1

*Many had practically normal renal studies before operation.

Observations on Renal Function in Prognosis

Good renal function is considered a prerequisite to sympathectomy. A study of the living patients was made to ascertain if a normal nonprotein nitrogen level, with moderate impairment of other renal-function tests, was a contraindication to surgery (Table 5). In many cases phenolsulfonphthalein thirty-minute excretion, urea clearance and specific gravity of the urine were not recorded.

In 26 of the 57 living patients with Grade 3 hypertension who were tested 15 to 40 per cent of the phenolsulfonphthalein was excreted in thirty minutes, whereas 31 excreted more than 40 per cent of the dye. The urea-clearance test was performed on 36 patients with Grade 3 hypertension who are still living and was less than 40 per cent in 1, between 40 and 75 per cent in 20 and over 75 per cent in only 15 patients. The specific gravity was less than 1.020 in 13 and more than 1.020 in 63 living patients.

Of the 16 patients with Grade 4 hypertension still living, the phenolsulfonphthalein excretion was determined in 14; it was less than 15 per cent in 1, between 15 and 40 per cent in 8 and over 40 per cent in only 5 patients. The urea clearance was less

Table 5. *Preoperative Renal-Function Studies in 89 Patients with Grade 3 and 16 with Grade 4 Hypertension Still Living.*

Classification of Hypertension	Phenolsulfonphthalein Excretion Less than 15%	Phenolsulfonphthalein Excretion 15 to 40%	Phenolsulfonphthalein Excretion More than 40%	Phenolsulfonphthalein Excretion Not Recorded	Urea Clearance Less than 40%	Urea Clearance 40 to 75%	Urea Clearance More than 75%	Urea Clearance Not Recorded	Specific Gravity Less than 1.020	Specific Gravity More than 1.020	Specific Gravity Not Recorded
	No. of patients	No. of patients	No. of patients	No. of patients	No. of patients	No. of patients	No. of patients	No. of patients	No. of patients	No. of patients	No. of patients
Grade 3	0	26	31	32	1	20	15	53	13	63	13
Grade 4	1	8	5	2	1	3	4	8	5	11	0

than 40 per cent in 1 patient, between 40 and 75 per cent in 3 and over 75 per cent of normal in 4 patients. The specific gravity was less than 1.020 in 5 and more than 1.020 in 11 patients. In both groups the ability of the kidneys to concentrate urine well seems to offer the best prognosis.

We have abandoned studies of blood-pressure lability as a valuable criterion to selection of patients for operation because we believe the operation should be done to prolong life in patients with Grades 3 and 4 hypertension who otherwise have a poor prognosis but whose kidney and cardiac function is still adequate enough to justify surgical intervention. These patients usually have fixed high levels of blood pressure, especially those with Grade 4 hypertension.

Discussion

That part of the title "with hemorrhagic hypertensive retinitis" is chosen with the thought that to the average clinician, and in actual fact, the development of hemorrhagic fundi is the best indication that hypertension is entering a serious phase, called "malignant" by some physicians. To classify cases as 1, 2, 3 and 4 (Keith, Wagener, and Barker[1]) or the four types of Smithwick[3] and Palmer and Muench,[12] although useful in the study of comparative results, leads to no hard-and-fast rules for the selection of patients according to the form of therapy to be adopted. Again, the dividing line between Classes 3 and 4 (Wagener–Keith–Barker) is too nebulous. The prognosis after splanchnicectomy or drug treatment depends more on kidney function than on the mere existence or absence of papilledema. The grave prognosis in Grade 4 hypertension is due to the rapid development of *necrotizing arteriolitis* in the kidneys.

In an experience of nineteen years with approximately 1200 splanchnicectomies for all grades of hypertension, we soon abandoned the operation for patients with Grade 1 disease, believing that the prognosis with proper rules of living was as good without operation as with it. Also, the morbidity after Poppen's section of the fourth thoracic through the second lumbar sympathetic ganglion and splanchnic nerves is too great to justify the procedure in patients with such mild disease. In the past four years we have abandoned the operation for patients with Grade 2 hypertension except those with symptoms of hypertensive encephalopathy, enlarged hearts or episodes of nocturnal orthopnea (failure of the left ventricle). We believe that many of the symptoms, such as transient hemiparesis and hypesthesias in patients with hypertensive encephalopathy, are a reflection in the cerebrovascular bed of what the physician sees in the retinal bed, small perivascular hemorrhages and edema, and although such findings are lacking in the retina, these cases to all intents and purposes should be classified as Grade 3. In patients with Grade 2 fundi and enlarged hearts we have advised splanchnicectomy because 90 per cent of such patients have subsequently had decrease in the transverse diameter of that organ — from 50 per cent to a normal cardiothoracic ratio.[10] However, no patients without hemorrhagic fundi are included in this study.

With the advent of modern drug therapy, especially in combinations, the indications for splanchnicectomy have further diminished, but to what extent is still an unsettled question. To us, it seems that the patient with hemorrhagic eye grounds and rapidly rising diastolic pressure, with or without coincidental papilledema, who is still young and who still has good kidney function, whose prognosis is statistically grave, with one to four years' life expectancy, is offered most by splanchnicectomy, then a low sodium diet if that is found necessary in subsequent months and then the addition of drug therapy. It is our experience and that of others that both these adjuncts are more effective after sympathectomy. There is no objection, if the patient insists, to trying a course of drug treatment first for two or three months, with the probability that these drugs will have to be taken and the blood pressure charted at home for the rest of his life. Indeed, it is becoming more and more difficult to persuade the patient of the necessity for a splanchnicectomy with its well known postoperative morbidity without a preliminary trial of the drugs. Because of the grave prognosis in most patients with hemorrhagic eye grounds, we believe so strongly that everything possible should be done that in 12 such patients who formerly would have been rejected for splanchnicectomy as hopeless, but who still had fair renal function, we removed one adrenal gland at the second-stage operation and were prepared later to perform a total adrenalectomy if the need arose. We advocate this procedure if congestive heart failure has been present because adrenalectomy profoundly influences sodium metabolism. In other words we take the stand that some of these patients may have a chance if we do everything in our power. No patient will be helped by any surgical procedure, however, unless he has enough glomeruli still functioning.

There are many patients in both groups with apparent "cures" of the disease. Many others feel well; their heart size has decreased, and their hemorrhagic retinitis cleared despite continued elevation of the blood pressure. There are many more who are given a few extra years of life in relatively good health even though they eventually succumb to the disease. Still another factor to be considered is that many patients respond more readily to the hypotensive drugs and low-sodium diet after sympathectomy.

The advent of the new hypotensive drugs raises a question that will take many years to answer: Is sympathectomy superior to drug therapy? Certainly,

these drugs are very useful for treatment of patients who would not be eligible for operation, and they may prove to be the treatment of choice for some who are otherwise candidates for sympathectomy. In many patients treated with these drugs the disease can be kept under good control, with improvement in cardiac and renal status and regression of hemorrhagic retinitis. Even if the results of drug therapy and surgery are the same, however, a sympathectomy may prove to be the treatment of choice in certain young patients with Grades 3 and 4 hypertension so that they may not need to be dependent on drugs for the rest of their lives. Also, the additional weapon of drug therapy would then be available if the hypertension recurred.

We are now averaging 1 splanchnicectomy every month or two on the neurosurgical service of the Lahey Clinic as compared with approximately 1000 done between 1942 and 1952. The principal reason for the drop in number of patients operated on has been the advent of the hypotensive drugs. If we could offer splanchnicectomy as a cure for hypertension, or if we could even select the patient who would obtain the occasional almost miraculous result seen after operation, we should still be doing more splanchnicectomies. Perhaps in time, unless something better comes along, we shall be doing more again for the patient under fifty-four years of age who is seriously ill with hypertension and who still has good renal function.

Summary and Conclusions

The survival rate up to ten and a half years was determined in 206 patients who underwent sympathectomy and splanchnicectomy, all of whom had hemorrhagic fundi (Grades 3 and 4 hypertension). Although the first patient was operated on nineteen years ago and the longest survival is fourteen and a half years, statistically reliable figures exist only for ten and a half years.

Patients with hemorrhagic fundi were selected for study because they most need salvage owing to their grave prognosis, and these cases most truly demonstrate any value of the operation.

The survival rate after operation on patients with Grade 3 and Grade 4 hypertension is compared with the expected survival rate for medically treated patients before the advent of the new hypotensive drugs. In the patients with Grade 3 disease the cumulative survival rate was 46 per cent in ten and a half years, compared with an expected survival rate of 0 per cent according to Keith, Wagener and Barker. The survival curve in these patients was based on cumulative figures, because this was the statistical method used by Keith, Wagener and Barker in their control series. Also, the patients in the group with Grade 3 disease corresponded most closely in selection to theirs.

In the patients with Grade 4 disease the relative survival rate was 39.9 per cent in six and a half years, compared with an expected rate of 5.6 per cent. At ten and a half years the survival rate was 33.4 per cent. The survival curves in these patients are the "relative survival" rate figures compared with expected survival (lx) by annual intervals beginning six months after classification for closer comparison with the survival curve of medically treated patients cited by Palmer and Muench before the advent of the newer hypotensive drugs. The patients with Grade 4 disease corresponded to theirs.

The operative mortality was 2 per cent in the patients with Grade 3 and 6 per cent in those with Grade 4 hypertension. Seventy-four per cent of the survivors among the former and 75 per cent of those among the latter felt well.

Blood pressure was reduced to a satisfactory level in 67 per cent of survivors with Grade 3 and 81 per cent of those with Grade 4 disease.

Cardiac status in patients with enlarged hearts or abnormal electrocardiograms was improved in approximately half the cases of Grade 3 and about a third of those of Grade 4 hypertension. Hemorrhages in the fundi disappeared in 84 per cent of patients with Grade 3 disease; and papilledema and hemorrhages disappeared in 100 per cent of those with Grade 4 hypertension.

Ability of the kidneys to concentrate urine to a specific gravity of at least 1.020 is apparently the best prognostic test for a good result in these two groups.

In spite of the advent of more efficacious hypotensive drugs than have hitherto been available splanchnicectomy is a valuable resort in patients with hemorrhagic fundi.

We are indebted to Dr. Hugo Muench and Miss Mary Alice Bowden, of the Department of Biostatistics, Harvard School of Public Health, and to Mr. Arnold W. Fieber, registrar of the Lahey Clinic, for their valuable help in compiling these statistics and preparing the survival curves and tables.

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THE TOXIC EFFECTS OF PHENYLBUTAZONE (BUTAZOLIDIN)*

Review of the Literature and Report of the Twenty-Third Death Following Its Use

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DRUGS employed in the past and at present for the relief of pain in the various forms of arthritis carry with them noxious traits that limit or prevent their use. Cincophen was abandoned because of its adverse effects on the liver. Cortisone has been responsible for serious side reactions, which have been limited by professional and public awareness of this drug's unwanted effects. Toxic reactions from gold have been held within bounds because it cannot be self-administered. Aminopyrine is no longer used because of its disastrous effects on the bone marrow. Today, phenylbutazone (Butazolidin), chemically similar to aminopyrine, is in wide use. To date 22 deaths following the use of this drug have been reported; this paper includes an account of the twenty-third.

FIGURE 1. *Appearance of the Patient during the Last Ten Days of Life.*

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CASE REPORT

A 48-year-old woman had taken 35 100-mg. tablets of phenylbutazone over a period of 22 days because of a painful knee. At this time a rash appeared: her physician discontinued this treatment and gave an injection of ACTH. Despite the prompt withdrawal of phenylbutazone nausea with vomiting, burning in the mouth with difficulty in swallowing and generalized aching appeared during the next 5 days. For these complaints she was admitted to the hospital.

On entry the temperature was 100.4°F., and there was a diffuse, blotchy, red rash, which spared only the face, and epigastric tenderness. The joints were not visibly affected with disease. Abdominal pain increased, and when rigidity of the upper abdomen developed laparotomy was advised since perforation of a peptic ulcer seemed likely. Surgical exploration revealed an acute ulcer in the 1st portion of the duodenum, but the bowel was intact. (Gastrointestinal x-ray study 2 years earlier had failed to show ulcer or spasm.) Soon, the rash became purpuric; the application of tourniquets for venipuncture caused marked diffuse purpura below the level of constriction. This capillary fragility was related to reduction in prothrombin, which was 17 per cent. Responses to whole fresh blood and vitamins K and K_1 were not satisfactory. The rash became polymorphic — morbilliform, purpuric and erythematous at various times. Severe membranous stomatitis developed. On the 8th hospital day blood smears yielded evidence of bone-marrow involvement, and on the 9th day the white-cell count was 28,200, with only 4 per cent mature leukocytes. Many immature forms were present. The bleeding time was within normal limits, and the coagulation time slightly prolonged; platelets and clot retraction were also within normal limits. On the 10th hospital day there was evident jaundice and severe intractable diarrhea began.

By the 12th day the skin had begun to exfoliate. This soon became generalized, with loss of large amounts of serum from the denuded areas. During the last 10 days of life the exfoliation involved the entire face, the neck, the thorax and all extremities (Fig. 1). The temperature was generally 100 to 103°F., but on the 22d hospital day it suddenly went over 108°F. The patient became comatose and died two days later, 28 days after the first sign of toxicity following the phenylbutazone therapy.

Treatment consisted of moist compresses to the skin, a peptic-ulcer regimen, antihistamines, maintenance of electrolyte homeostasis, blood transfusions, injections of concentrated human albumin, ACTH and, later, cortisone. All treatment was unavailing, and the various evidences of toxicity unfolded without hindrance.

Autopsy revealed the extensive loss of skin already described. The duodenal ulcer seen at operation was no longer visible. There were a number of superficial erosions, 1 or 2 mm. in diameter, in the mucosa of the stomach, sigmoid colon and rectum. The liver weighed 1300 gm. and was soft and yellow. There were no other gross findings of significance.

On microscopical examination the liver cords were markedly distorted and irregularly necrotic. Although necrosis seemed more severe toward the center of the lobule it was not of zonal distribution. Many of the cells showed fatty vacuolation. Regeneration was not seen (Fig. 2). There was no polymorphonuclear infiltration, but a few plasma cells and histiocytes were present.

The bone marrow disclosed marked reduction of the granulocytic series, with absolute neutropenia and a relative increase in monocytes and plasmacytes. The erythrocytic series did not appear altered.

Death was due to an acute necrotizing process characterized by infiltration of plasma cells and histiocytes, with little or no infiltration of neutrophils or eosinophils in the various organs studied. This process involved the skin, causing exfoliative dermatitis; the liver, leading to diffuse toxic hepatitis; and the colon, causing mucosal necrosis and superficial ulceration. Similar lesions were present in the vagina, urinary bladder and elsewhere in the intestinal tract. Unfortunately, the portion of the stomach containing the ulcerations seen grossly was not available for microscopical examination. There was infiltration of the adrenal glands and the kidneys with histiocytes and plasma cells, but in these organs there was no necrosis.

Review of the Literature

Even in the early and enthusiastic reports, there was a good deal of interest in the toxicity of phenylbutazone, presumably because of its resemblance to aminopyrine. Reactions were for some time regarded as minor and when encountered were charged to the simultaneous use of other drugs, "in one case an enema and in another phenobarbitone." Morphine, codeine, iodoform and shellfish were also indicted in these papers.[1,2] Kuzell and his co-

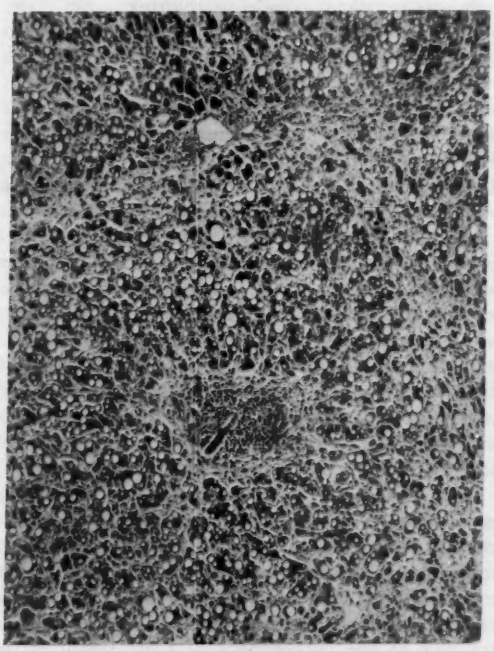

Figure 2. *Photomicrograph of a Section of the Liver.*

workers,[3] in their first report on phenylbutazone, ascribed some of the reactions to the presence of coexisting diseases. In this, the first extensive report, which dealt with 140 patients, the authors observed 47 toxic reactions and were forced to discontinue treatment in 17 of them. Nevertheless, they concluded that phenylbutazone was a safe drug. Succeeding publications of all shades of opinion concerning the usefulness of phenylbutazone dealt at unusual length with its toxicity. Some depreciated and others emphasized the significance of these reactions.

Table 1 summarizes the reports of toxicity in 26 papers,[1-31] which describe the effects of treatment in groups of 15 to 800 patients. This series consists of 3934 patients, of whom 1199 exhibited 1543 reactions of varying degrees of severity, from easily reversible water retention to death. The reaction rates observed by various authors differed enormously: Shulman[10] noted only "a few rashes" in 237 patients whereas Granirer[20] was forced to discontinue treatment in all the 20 cases that he reported. Kuzell and his associates[4] observed 457 reactions in 321 of a series of 800 patients. The necessity for discontinuance of treatment because of apparent toxicity was likewise disparate. Byron and Orenstein[22] found it necessary to stop treatment in only 9 per cent of 131 patients, but Nassim and Pilkington[16] had to discontinue the medication in 42 per cent of 109 patients. The papers reviewed failed to reveal any reasons for these wide discrepancies in the dosage of phenylbutazone used, ages of the patients or conditions treated.

Table 1. *Summary of Toxic Reactions to Phenylbutazone.*

Reaction	No. of Cases
Acute peptic ulcer (8 bleeding & 1 perforated)	22
Reactivated peptic ulcer (6 bleeding)	18
Gastrointestinal bleeding (source unknown)	9
Upper gastrointestinal symptoms (nausea, vomiting, pain etc.)	415
Diarrhea	22
Toxic hepatitis	2
Rashes	191
Stomatitis, dry mouth	96
Agranulocytosis	6
Leukopenia	32
Purpura	13
Thrombocytopenia	32
Edema	337
Cardiac decompensation & pulmonary edema	13
Miscellaneous	332
Death	3

In an effort to gain more detailed information about the toxicity of phenylbutazone, the case reports of such reactions were reviewed. The discussion that follows is based largely on them. In some the information is meager, but in most the details of dosage and duration of treatment and the clinical manifestations of the reactions provide information on which certain conclusions presently may be based.

The case reports yielded 19 additional deaths, which, with the present case and the 3 from Table

1, give a total of 23 deaths attributed to the use of phenylbutazone (Table 2). Forty-nine severe but nonfatal reactions were also reviewed. These, along with the deaths, are listed in Table 2 under the entity regarded as the major reaction. The present case is listed with the agranulocytoses.

Agranulocytosis

Agranulocytosis,[32-54] the most frequent complication found in the case reports, occurred at various times from the seventh to the sixtieth day of treatment. There was no apparent relation to dosage, which ranged in total amount from 3.5 to 39.2 gm. There were 10 deaths,[36-39,41-43,46,49] including the case reported above, in which granulocytic depression oc-

TABLE 2. *Types of Fatal and Nonfatal Reactions to Phenylbutazone.*

REACTION	DEATHS	RECOVERIES
Agranulocytosis	10	15
Aplastic anemia	1	—
Thrombocytopenic purpura	1	—
Peptic ulcer & gastrointestinal hemorrhage	3	12
Renal lesions	2	1
Exfoliative dermatitis	3	5
Rashes & stomatitis	—	4
Toxic hepatitis	1	12
Unclassified	2	—

curred between the eighth and the sixtieth day. Of major interest was the relation of the rash to the development of agranulocytosis. Rashes were noted in almost all the cases in which agranulocytosis developed during the first four weeks of treatment. The skin reactions preceded changes in the blood by intervals of four to fifteen days. It is most important to recognize this sequence of events, for rashes have previously been regarded as "minor" evidences of toxicity. It has been stated that the rashes subside after cessation of therapy and that in most cases they will not recur after resumption of treatment at lower dosage levels.[3,4,50,55] It appears to be a dangerous practice to administer phenylbutazone while undetectable but serious changes are occurring in the bone marrow. After the fourth week agranulocytosis appeared without benefit of cutaneous warning in the 11 cases that developed between the twenty-eighth and the sixtieth day, and 5 of these patients died.

As with other drugs known to suppress the bone marrow periodic blood counts have been advised. In many of the cases reported this was not done. If such surveillance was possible it is not likely that agranulocytosis could be prevented. Weekly blood counts failed to give warning of impending agranulocytosis in the patients of Etess and Jacobson[36] and Steinberg et al.[37] In the case presented above, the peripheral blood did not give evidence of bone-marrow involvement until about two weeks after medication was stopped. Kersley and Mandel,[48] Hart[7] and Pemberton[17] are in agreement on the futility of blood counting as a protective measure, pointing out the progression of bone-marrow depression even after withdrawal of phenylbutazone and the dramatic suddenness with which complications may appear in some patients under close observation. Delay in the appearance of the reaction is undoubtedly related to the persistence of the drug in the blood for long periods after the last dose. This characteristic of phenylbutazone is discussed further below.

Two other fatal blood dyscrasias occurring in relation to phenylbutazone therapy were reported, 1 of aplastic anemia[40] after two weeks and 1 of thrombocytopenic purpura[56] after about ninety days of treatment.

Gastrointestinal Complications

In the reports reviewed there were 15 cases of severe gastrointestinal reactions. Four of these were acute gastric ulcers, single or multiple. Of these, 3 bled,[39,57,58] and 1 perforated.[59] There were also 4 acute or subacute duodenal ulcers. One of these bled,[59] and three perforated.[59-61] Of the 8 patients with acute or subacute ulceration, 3 died — 2 of perforation, and 1 of hemorrhage. The patient of Beutler and Bergenstal,[61] who died of perforation of an acute duodenal ulcer, also suffered severe neutropenia. Siguier[62] described 3 patients in whom it was thought that pre-existing ulcers were reactivated by phenylbutazone; he observed, as others had, that parenterally administered phenylbutazone could apparently produce peptic ulceration. Three of the remaining patients in this group had melena,[51,63] and the last[63] vomited blood. In none of these was the source of bleeding found. Here, again, latency of reaction was observed, for in 2 patients with gastric ulceration[58,59] symptoms began several days after phenylbutazone was discontinued.

This group of complications appeared from the seventh to the thirty-fourth day with total dosage varying from 4 to 17.2 gm. As shown in Table 1 there were 9 other cases of bleeding from unknown sources and 22 patients with diarrhea. The enteric lesions found in 3 of the autopsied cases may provide the clue to the pathogenesis of these symptoms of toxicity. The diarrhea observed in the case reported above was in all likelihood the result of the ulcerations present in the sigmoid and rectum. In 3 other autopsied cases small ulcerations were found. Dilling's[46] patient with fatal agranulocytosis revealed about a hundred superficial erosions, 1 to 5 mm. in diameter, in the stomach. In another fatal case of agranulocytosis[15,42] small ileal ulcers were found. Nathan et al.[64] discovered similar lesions in the stomach and jejunum in their fatal case of exfoliative dermatitis. Such small superficial erosions of the

gastrointestinal mucosa cannot be visualized on x-ray examinations but could most certainly produce pain, bleeding or diarrhea.

Hepatic Lesions

Thirteen cases were reported in which the primary diagnosis was jaundice or toxic hepatitis occurring in relation to phenylbutazone therapy.[65-69] One of these patients died of toxic cirrhosis.[68,70] In another, biopsy revealed focal necrosis.[66] Liver involvement appeared from the third to the fortieth day with total doses of 1.5 to 32 gm. Unfortunately, in most of these reports, prothrombin levels are not available. But purpuric manifestations are often encountered in the reports on patients who have no deficiency of platelets or abnormalities of bleeding or clotting. The patient described above had severe spontaneous purpura and greatly diminished capillary resistance that were due to the hepatic lesion and the associated poverty of prothrombin. Humble[71] had previously observed, in studying patients who demonstrated reduced capillary resistance during phenylbutazone therapy, that there was a reduction of the prothrombin content of the blood and that this could be corrected by vitamin K_1 oxide. Unfortunately, in the case reported above, liver damage was so extensive that only a slight rise in prothrombin resulted from this therapy. Brodie et al.[27] later studied a group of 16 patients to determine the effects of phenylbutazone on the prothrombin content of the blood. They found it unaltered, but none of their patients had liver damage from the drug. Since phenylbutazone does not have antiprothrombin properties as anticoagulants such as Dicumarol do, their findings seem reasonable, but it is equally reasonable to expect a change in prothrombin content when there is cellular damage in the liver, whether it is due to phenylbutazone or to any other agent.

Renal Complications

Among the miscellaneous reactions listed in Table 1 there were 14 cases of hematuria. Although this did not appear in any of the case reports as an isolated reaction of toxicity 2 fatal reactions were ascribed to renal damage from phenylbutazone. The patient described by Bruck et al.[14] was treated for about twenty-eight days with a daily dose of 600 mg. After this he became ill, manifested hematuria and oliguria and died in uremia twenty-six days after medication was stopped. Autopsy showed degeneration of the convoluted tubules and fatty changes in the liver. The authors stated that there was no direct evidence of phenylbutazone toxicity but thought it quite likely that the salt-retaining effect of the drug had precipitated oliguria and renal failure. In the other fatal case,[72] which occurred in a patient with gout, 400 mg. three times a day was given. After a total dosage of 3.2 gm. medication was stopped because of hematuria. The patient became oliguric and then anuric and died eleven days after the first dose. Autopsy revealed acute hydronephrosis, with ureters plugged with uric acid crystals. Death in this case was thought to have been due either to the uricosuric action of phenylbutazone or to the production of highly concentrated urine secondary to the sodium-retaining properties of the drug. Another patient,[73] who took only 1.4 gm. over a three-week period, recovered after an episode of anuria; in this case renal biopsy demonstrated necrosis of the convoluted tubules.

Mucocutaneous Reactions

There were, in addition to the description of rashes associated with agranulocytosis, 12 reports of reactions in which the major disturbances were confined to the skin and mucous membranes.[51,67,74-80,64,81,82] Ten of these reactions occurred during the first seventeen days of treatment, 1 after thirty days, and another after intermittent dosage for a year. Three of the patients in this group died of exfoliative dermatitis or of erythema multiforme bullosum. One patient[80] took 100 mg. four times daily until she had completed her prescription of 50 tablets; five days later she became ill and died soon after of sepsis secondary to severe exfoliation. Another[64] died of exfoliative dermatitis after taking 13.6 gm. in seventeen days. The third death[82] was due to erythema multiforme bullosum and followed a year of intermittent treatment with doses of 200 to 300 mg. daily. Among the patients who recovered a number were acutely ill for long periods. The patient of Fishman and Reynolds,[76] in addition to severe exfoliation, gave evidence of bone-marrow involvement. In this woman recovery was delayed for seven months. Other patients were acutely ill for four to six weeks. Latency of reaction was a feature in 2 patients — that of Cone et al.,[80] already described, and also in the case reported by Steel and Moffatt,[78] in which medication was stopped because of relief of symptoms; four days later there was stomatitis followed by a bullous eruption, which desquamated. Although this patient's bone marrow revealed maturation arrest, there was healing of the skin lesions by the fourth week and eventual recovery. Eight of the 12 patients in this group exhibited exfoliative phenomena. Systemic evidence of toxicity was common in the others, whose skin did not peel. Fever, adenopathy, stomatitis and leukopenia were noted in varying combinations in these patients.

Unclassified Deaths

The patient described by Davies et al.[15] died after nine days of treatment and had fever, lymphadenopathy and convulsions. In the remaining fatal case[60] the diagnosis of phenylbutazone intoxication was

based solely on the history of ingestion of the drug. Autopsy revealed unexplained gas gangrene, which made an exact pathological diagnosis impossible.

Kelly's[30] paper described 5 deaths during or after treatment that were not included in the cases summarized above:

> Five early patients died. Two at the ages of 88 and 73 developed heart failure and one aged 76 had chronic bronchitis. A previously anemic patient died from hemolytic anemia after a year, and a chronic nephritic boy died 6 weeks after treatment was stopped.

Miscellaneous Reactions

Water retention was noted in 337 of the patients listed in Table 1. Of this group 13 cases were described under various but related headings, such as cardiac decompensation, pulmonary edema, hypertension and dyspnea and other symptoms referable to the cardiovascular system. (I have seen 1 patient in whom remission of refractory congestive heart failure and reduction of blood pressure from high to normal levels occurred after withdrawal of phenylbutazone.) Fever, various subjective nervous-system symptoms and visual symptoms were also described. The last should be regarded with some concern, for Engleman[63] has described 2 patients with optic neuritis that was thought to be a toxic effect of phenylbutazone.

Analysis of Factors That May Affect Reactions

Dosage. After the recognition of toxic reactions to phenylbutazone, the recommended daily dosage was reduced from about 800 mg. to 1 gm. to the present levels of 300 to 400 mg., and the manufacturer halved the size of the tablet to its present form, 100 mg. Nevertheless, there have been 7 deaths,[37,41,42,61,80,82] including the case presented above, in which the dosage never exceeded 400 mg. daily. Ten deaths occurred in patients who at no time took more than 600 mg. daily. Nonfatal agranulocytosis, ulcers with hemorrhage and perforation, toxic hepatitis, anuria and serious skin disturbances have followed daily dosages between 300 and 400 mg.[34,48,58,59,68,72,77,81] Total dosage for the patient treated intermittently for a year[82] could not be calculated, but in 8 patients the total dose ranged from 1.2 to 8 gm.; in 4 it was 10 to 14 gm.; 1 took 18 gm. and the remaining patient in this series 25 gm.

Duration of treatment. Although it has been stated that most reactions occur during the first five weeks of treatment[30] tolerance for this period does not preclude the possibility of reactions. As shown, deaths have been reported in the second, third and twelfth months of treatment. There seems to be little choice between constant and intermittent treatment since fatal reactions have resulted from each method.

In this connection the statements of deSèze[84] and Belart[85] are of interest. deSèze treated 700 patients parenterally and had only 6 reactions, 4 with gastrointestinal bleeding and 2 with "blood dyscrasias." Belart treated "about 1000" patients by the same means and reported only 10 reactions: 1 with gastric bleeding, 2 with purpura, 3 with hematuria and 4 with angioneurotic edema. He stated that there were fewer reactions on the Continent than in Great Britain or the United States because Butapyrin was given by intramuscular injection. This product contains 750 mg. each of aminopyrine and phenylbutazone. Belart considered injection of Butapyrin to be safer because treatment with tablets is continuous and of longer duration and secondly because, as phenylbutazone combines with protein, "when the drug is given by mouth this change takes place in the blood; when it is injected intramuscularly however, the change occurs in the muscle protein." This unique pharmacologic concept was not supported by the findings of Kidd et al.,[21] who reported undesirable effects in 68 per cent of patients treated with Butapyrin as compared to 26.7 per cent treated with phenylbutazone in their series.

Age. It has been claimed that "susceptibility to reactions increases sharply with increasing age."[86] Kelly[30] reported that 45 per cent of toxic reactions occurred in patients over sixty-five years of age and concluded in this regard that phenylbutazone is a safe drug if not given to persons over that age. However, it should be noted that 18 of the 23 deaths reviewed in this paper occurred in patients in Kelly's permissive age group. There was 1 death in the third and 1 in the fourth decade, and 5 each in the groups forty to forty-nine, fifty to fifty-nine and sixty to sixty-four, as well as 1 at sixty-five years of age. The remaining 5 deaths were in patients between seventy-one and seventy-eight.

Prevention. It has already been shown that periodic blood counts cannot predict serious or fatal changes in the bone marrow in patients who have been given phenylbutazone. The occurrence of reactions that have their onset after cessation of treatment, of course, defies prediction. Six patients who stopped medication because of relief of symptoms,[58,78] lack of effect,[38,59] a cold[65] or depletion of prescription[80] suffered serious toxic reactions four to six days later. Two of these patients died.[38,80] Seven patients, including the one described above, discontinued medication because of abdominal symptoms or rashes,[37,45,48,49,68,73] and more serious reactions developed later. Five patients, including the present patient, became agranulocytic[37,45,48,49]; the interval from first reaction to agranulocytosis was four to fifteen days. One of these patients, in addition to the patient described above, died.[37] Anuria[73] and toxic hepatitis [68] developed three and ten days after the last dose of phenylbutazone. As Bruck et al.[14] have shown, phenylbutazone remains in the blood for ten to twenty-one days after cessation of treatment. The

duration of treatment does not influence the degree of persistence of the drug in the body. This retention in the body undoubtedly causes the delayed reactions and the aggravation of some of the "mild" reactions. In the patient of Hinz et al.[34] phenylbutazone was present in the blood fifteen days after the last dose; in the fatal case reported by Nathan and his associates[64] the plasma level was 15 mg. per liter eight days after discontinuance of therapy.

If, then, it is not possible to predict disastrous damage to the bone marrow by routine blood counts and if, as shown, toxic reactions develop after cessation of medication, it appears likely that there is no present method of anticipating serious complications of therapy with phenylbutazone.

Discussion

It is of the utmost importance to recognize the serious, unpredictable and often irreversible accompaniments of the use of phenylbutazone. Physicians are importuned by advertisements and gratuitous reprints to use this drug in a large variety of conditions: gouty arthritis, rheumatoid arthritis, osteoarthritis, psoriatic arthritis, spondylitis, fibrositis, bursitis, scapulohumeral periarthritis, myositis, neuralgia and sciatica. This list is taken from an advertisement. If the drug had curative powers in any of these conditions, a modicum of risk might be justified. But phenylbutazone must be recognized for what it is, an analgesic somewhat similar to the abandoned aminopyrine. It behooves the practitioner to apply to the appraisal of phenylbutazone the same criteria with which he judges other drugs. The literature of phenylbutazone contains a number of statements that place the responsibility for serious and typical reactions on concomitant medication or upon the vices of the patient[1,2,86] or on the presence of coexisting diseases.[8,80] That the drug is toxic is now evident, and a far greater awareness of the risk taken in its use is warranted not only by the deaths that have been reported but also by the long-continued morbidity and the suffering and economic hardship entailed in the slow and painful recoveries of some of the more fortunate victims of the toxic properties of phenylbutazone.

Summary and Conclusions

The twenty-third death following the use of phenylbutazone, a drug resembling aminopyrine in chemical structure, is reported. The literature concerning the toxicity of this drug is extensive, and serious reactions have been encountered in the skin, gastrointestinal tract, liver, kidney and bone marrow, as well as in other organs. These reactions do not appear to be related to dosage or duration of treatment. They may occur after the drug has been withdrawn. There are no known methods of predicting an impending reaction. At present there are no specific means of treating reactions that have appeared.

It is concluded that the use of phenylbutazone, which has apparently no curative powers, should be carefully restricted because of the frequency of toxic reactions, their gravity and the unpredictability of their occurrence.

Since completion of this paper another hitherto unrecorded fatal case has been made available through the courtesy of Dr. Arthur M. Hoffman. A seventy-eight-year-old man demanded, and received (from an outpatient department) treatment with phenylbutazone. He took 100 mg. three times a day for two weeks, after which he died of gastric hemorrhage. Three acute ulcers were found in the stomach at autopsy. Previous x-ray studies had not revealed gastric disease.

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ESTROGEN AND COMBINED ESTROGEN AND X-RAY THERAPY*

Their Effects on Advanced Malignant Salivary-Gland Tumors

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RECENT clinical experience with malignant tumors of salivary-gland origin has demonstrated that this form of cancer may be favorably influenced either by hormones or by the combination of hormone and x-ray therapy. Healing of ulcerated lesions and tumor regression have been observed after administration of estrogen alone. Relief of pain and improvement of the patients' general status have also been noted. Similar responses have occurred when the disease has been subjected to x-ray therapy in patients who were currently under estrogen treatment.

This clinical experiment is based on observations made by Nathanson and White[1] after x-ray therapy of breast cancer undergoing hormone treatment. Some of the patients receiving estrogens for advanced breast carcinoma were subjected to irradiation when the disease showed reactivation. The response to nominal quantities of x-ray therapy was quite marked, and a surprising degree of tumor regression was noted. Continued investigation led to the conclusion that increased radiation response could be induced in breast carcinoma by prior administration of estrogen.

The application of these experiences to salivary-gland cancer was prompted by the observations of

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sex difference in the submaxillary glands of laboratory animals. Sex dimorphism of the submaxillary gland in mice and rats has been described by Fekete.[2] Frantz and Kirschbaum[3] also showed that the gland could be altered by androgen injection into the castrated female, or by castration in the male. Fogg and Cowing[4] demonstrated that the submaxillary gland of the castrated male mouse became feminized in four to six weeks. Although we are not aware of any recognizable sex difference in the human salivary gland we were encouraged to attempt hormone therapy on a theoretical basis. The parallel experiences with breast and salivary-gland cancer as affected by estrogen lend strong support to the thesis of sex influence in the human salivary gland.

TABLE 1. *Site and Histology of Salivary-Gland Tumor.*

CASE NO.	PATIENT	HOSPITAL NO.	SEX	AGE	ORIGIN OF TUMOR	SITE OF DISEASE TREATED	HISTOLOGY
				yr.			
1	E.I.	P.H. 25994	M	58	Probably small salivary glands in floor of mouth	Floor of mouth	Papillary adenocarcinoma of salivary duct
2	M.A.S.	P.H. 27771	M	61	Left side of neck	Pulmonary metastases	Carcinoma, probably arising from salivary gland
3	M.L.S.	P.H. 29255	F	54	Right parotid gland	Right parotid gland	Carcinoma
4	J.M.	P.H. 30310	F	81	Right maxillary region, palate & nares	Right maxillary region, palate & nares	Low-grade adenocarcinoma of salivary-gland origin
5	J.O'D.	P.H. 30934	M	48	Left parotid gland	Left parotid gland, neck & submental regions	Adenocarcinoma of parotid gland
6	J.M.F.	P.H. 34174	F	74	Right parotid gland	Right parotid gland	Epidermoid carcinoma
7	G.C.P.	B.V.A.H. 12626	M	28	Right parotid gland	Right parotid gland — postoperative recurrence	Malignant mixed tumor (pulmonary metastases)
8	H.R.	B.V.A.H. 11809	M	56	Left parotid gland	Left parotid area (skin) & right submaxillary lymph nodes	Adenocarcinoma

TABLE 2. *Results of Therapy.*

CASE NO.	DAILY DOSE OF ESTROGEN	PRERADIATION PERIOD OF HORMONE TREATMENT	RESPONSE TO ESTROGEN	X-RAY THERAPY		RESPONSE TO X-RAY THERAPY	REMARKS
				DOSE‡	DURATION		
				r	days		
1	10-20 mg.*	6 mo.	Minimal; fungating mass became cleaner.	2400	12	Excellent; almost complete healing in 3 wk.	
2	10-15 mg.*	5 wk.	None	None		—	Patient died 6 wk. after hormones started & was moribund during treatment
3	15 mg.*	None (given with x-ray therapy)	—	6800	24	Partial regression in 3 wk.; complete regression in 3 mo.	Patient died of probable intracranial extension
4	15 mg.*	4 mo.	Moderate; tumor size decreased.	2200	12	Complete regression 6 wk. after radiation	
5	15 mg.*	1 wk.	None	2100	12	Excellent; marked regression of disease.	Duration of response, 4 mo.; estrogen poorly tolerated.
6	20-30 mg.†	None (given with x-ray therapy)	—	3000	14	Considerable regression 6 wk. after radiation	Disease progressed in other sites
7	30 mg.*	10 days	None	3000	14	Marked decrease in tumor size, with relief of pain	Patient gained 15 pounds after treatment, but died of intracranial extension
8	40 mg.*	7 mo.	Excellent; complete regression of metastatic lymph nodes & marked decrease in skin recurrence.	1500	5	Excellent; complete regression of reactivated lymph nodes & skin recurrence.	Duration of estrogen effect, 7 mo.; x-ray therapy given for reactivation of disease.

*Diethylstilbestrol.
†Diethylidene-ethylene diphenol.
‡Measured in air.

Eight patients have been treated by estrogen and x-ray therapy, and the type and location of the disease is noted in Table 1. Four patients had carci-

noma arising in the parotid gland (Cases 3, 5, 6 and 8). Three patients had carcinoma that was apparently of salivary-gland origin although not originating from any of the large glands (Cases 1, 2 and 4). One patient had a malignant type of mixed tumor that metastasized to the lungs (Case 7).

The results of treatment are listed in Table 2. One of the principal difficulties in this type of clinical investigation is the determination of effective estrogen dosage. Initially, most of the patients received nominal amounts of estrogen. Subsequently, experience indicated that high doses were probably necessary if any response to the hormone alone was to be obtained. The reluctance to withhold x-ray therapy in patients with advanced disease led to early x-ray treatment, which precluded any lengthy observations of possible effects of estrogen alone. Many of the patients received substantial doses (2100 to 3000 r in air), and 1 patient received 6800 r in air to the area of disease. Responses to this amount raise the question whether the tumors might have responded as well to x-ray therapy alone. However, the last patient treated (Case 8) had a remarkable response to both estrogen alone and, later, combined estrogen and x-ray therapy. An abstract of this case follows:

Case Report

Case 8. H.R. (B.V.A.H.#11809), a 56-year-old man, had a large adenocarcinoma of the left parotid gland removed, with radical neck dissection, in December, 1953. Twelve out of 12 lymph nodes in the neck were positive for metastases.

Phase 1 (Hormone Therapy)

On June 15, 1954, there were extensive skin recurrences and multiple palpable metastatic lymph nodes in the right side of the neck. Diethylstilbestrol, 40 mg. daily, was given. Two weeks later the lymph nodes were smaller and softer; skin recurrences were cleaner and less marked. The hormone was continued.

On August 8 partial epithelization of the skin defects was noted. There was clean, dry crusting formation in other areas. On November 3 all skin ulcerations were fully epithelized. No palpable lymph nodes could be felt in the neck. The hormone was continued in amounts of 40 mg. daily.

On January 19, 1955, there was reactivation of the disease in the lymph nodes and skin.

Phase 2 (Added X-ray Therapy)

On February 1, 1500 r, measured in air, was given in 5 days to the lymph nodes and areas of skin recurrence. The hormone was discontinued on the day of the last treatment. Three days later a brisk skin reaction and epithelitis were observed. On March 2 there was an excellent response to radiation, with complete regression of the lesions of the skin and lymph nodes.

The response of the ulcerated skin surfaces was very similar to that noted during hormone treatment of ulcerating breast cancer — namely, regression of disease, crusting and epithelization.[5] The remission noted under estrogen therapy alone lasted for a period of 7 months, and the disease then appeared to escape the estrogen effect. The added x-ray therapy resulted in prompt remission, and, to date, there has been no recurrence in the treated areas. New foci of activity have appeared in other sites, and the whole regimen will be repeated in an effort to obtain similar responses.

Discussion

Our limited experience in this group of patients has evolved a general plan of treatment that we hope to carry out in the future. When hormones are administered the patient should be observed for at least a month for hormone effect alone before the addition of x-ray therapy is considered. If the response to estrogen becomes evident, the patient should be continued on the same regimen until any signs of reactivation occur, when nominal amounts of x-ray therapy may be added and the hormones discontinued on the day of the last treatment.

Summary

Advanced tumors and cancer of salivary-gland origin were favorably affected by either estrogen therapy alone or by the combination of hormone and nominal amounts of x-ray therapy. The results were most encouraging and were considered to warrant continued clinical investigation of this mode of therapy.

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Boston 15

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SPECIAL ARTICLE

IDIOPATHIC PULMONARY HEMOSIDEROSIS*

Report of a Case in Early Childhood with Severe Anemia

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PULMONARY hemorrhage of unknown etiology is a rarely reported cause of childhood anemia. In this condition iron pigment from red-cell breakdown is trapped by local histiocytes, resulting in brown induration of the lung. This disease, which is often not diagnosed during the lifetime of the patient, is known as idiopathic pulmonary hemosiderosis and has been well described by Wyllie et al.[1] It either follows an insidious course, suggesting chronic anemia, or is marked by acute episodes of hemorrhage, with resulting pallor, fever, abdominal pain and vomiting. Physical examination of the chest in fully developed cases may be negative, but x-ray studies show a flecklike reticular pattern, most prominent in the lower lobes and hilar areas; early in the course of the disease these findings may be absent. During acute attacks superimposed mottled densities appear, suggesting bronchial infection. As these lesions evolve tuberculosis or any of the granulomatous diseases may be considered on examination of the chest films.[2-4] The blood picture is that of an iron-deficiency anemia that frequently develops hemolytic features.

The following case, diagnosed at autopsy, illustrates many of the aspects of an acute form of this disease, and is the sixth report from North America.[5-9]

CASE REPORT

A male Negro infant weighing 2.1 kg. (4 pounds, 11 ounces) was born in the hospital on July 24, 1950, by normal spontaneous delivery during the 8th month of gestation. No abnormalities were noted, and the patient was discharged 1 month later after having gained 0.5 kg. (1 pound). He was placed on an evaporated-milk formula and multivitamins, with the addition of a preparation containing iron and copper. He was seen in the clinic at the age of 3 months, when he was well and weighed 3.8 kg. (8 pounds, 6 ounces).

The patient was next seen on June 21, 1951, at the age of 11 months, when he was admitted to the hospital because of cough, fever, grunting respirations, lethargy and vomiting, which had developed over the previous 3 days. Two siblings, aged 2 and 3 years, were in good health. The past history revealed no previous illnesses but indicated that the patient's diet had been deficient in eggs, meat, vegetables and supplemental vitamins.

Physical examination showed an acutely ill boy with a temperature of 102.4°F. by rectum and rapid grunting respirations. The mucous membranes and conjunctivas were very pale. The heart was not remarkable except for tachycardia. The liver was not enlarged, and the spleen was not felt. Examination of the blood disclosed a red-cell count of 1,610,000, with a hemoglobin of 2.0 gm. per 100 cc., and a white-cell count of 34,000, with 50 per cent neutrophils, 49 per cent lymphocytes and 1 per cent basophils. The hematocrit was 11 per cent, the mean corpuscular volume 69 cubic microns, the mean corpuscular hemoglobin concentration 33 per cent, and the mean corpuscular hemoglobin 26 micromicrogm. The total serum bilirubin was 1.6 mg. per 100 cc., with a direct value of 0.3 mg. per 100 cc. Sickle-cell preparation and a flocculation test for syphilis were both negative. The peripheral smear showed microcytic hypochromic anemia, with polychromasia and frequent normoblasts. The urine was straw colored and negative for sugar and albumin. X-ray examination of the chest (Fig. 1) revealed diffuse, slight mottling throughout both lung fields and a 3-cm. patchy density in the right lower lung suggesting pneumonia. A diagnosis of iron-deficiency anemia and bronchopneumonia was made, and the patient was treated with whole-blood transfusions, penicillin and ferrous sulfate. Two days after admission the temperature returned to normal. The tuberculin skin test was negative. He was discharged on July 3, with a hemoglobin of 9 gm. per 100 cc. Iron, liver extract and multivitamins were prescribed on discharge.

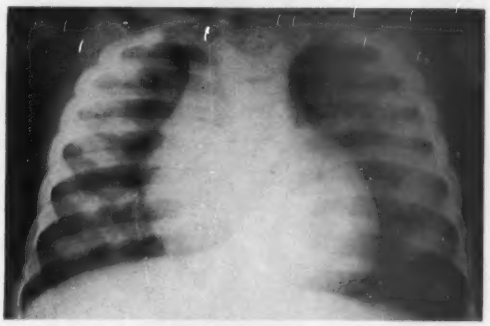

FIGURE 1. *Roentgenogram of the Chest, Showing Diffuse Mottling throughout Both Lung Fields after an Acute Episode That Was Thought to Represent Widespread Pulmonary Hemorrhage.*

On readmission 2 months later it was ascertained that in the interval the patient had appeared well and gained weight, but that, 3 days before admission, he had become drowsy and anorectic and appeared to have difficulty breathing. Physical examination revealed a well developed boy weighing 8.8 kg. (19 pounds, 6 ounces) who was somewhat listless but in no acute distress. The temperature was 100.4°F. by rectum. The scleras were icteric, and the oral mucosa was pale. Fine rales were present in both lung fields, and an apical systolic murmur was heard. The spleen and liver were not felt; there was no lymphadenopathy.

Examination of the blood disclosed a hemoglobin of 5.5 gm. per 100 cc. and a white-cell count of 11,750, with 34 per cent neutrophils, 64 per cent lymphocytes, 1 per cent eosinophils and 1 per cent monocytes; the reticulocyte count was 18 per cent, and the total bilirubin 2.5 mg. per 100 cc., with a direct value of 0.5 mg. per 100 cc. The

*Student essay (first prize) from the Medical College of Virgina. The work on which this paper is based was carried out during the course of an externship in pathology at the Medical College of Virginia.

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bone marrow showed marked erythroid hyperplasia. Bleeding and clotting times were normal. Maximum red-cell fragility occurred in 0.32 per cent saline solution. The sickle-cell preparation was again negative. The urine was brown, and a 50-cc. specimen contained 0.5 mg. of urobilinogen. On the day of admission 75 cc. of whole blood was given. A chest film 2 days later showed bilateral hilar and peripheral densities that were thought to be compatible with bronchial infection.

During the following 2 weeks the patient was afebrile, and additional studies were carried out. The direct Coombs tests was negative. Stool specimens were positive for occult blood by the Meyer and guaiac tests, and negative for parasites and ova. X-ray examination of the skull and long bones showed no changes to suggest vitamin deficiency or hemolytic anemia. The mother's blood was studied and revealed an iron-deficiency anemia of moderate severity. On October 4, 24 days after admission, the patient's hemoglobin had risen to 10.0 gm. per 100 cc. He received a transfusion that morning, consisting of 130 cc. of whole blood, which he took without reaction. That evening the temperature rose to 101.4°F. by rectum, and plans for discharge were cancelled. The respirations were 65. X-ray study of the chest on the next day showed patchy densities throughout both lung fields. Antibiotics were started.

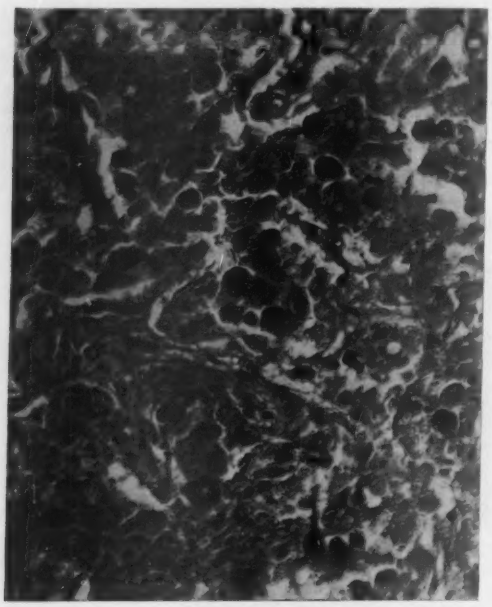

FIGURE 2. *Section of the Lung (Hematoxylin and Eosin Stain X 225), Showing Numerous Pigment-Filled Histiocytes in the Alveoli.*

During the following week the patient ran an intermittent low-grade fever, the maximal reading being 100.6°F. The respiratory rate was considerably elevated during this period. The urine on October 8 was tea colored. On the following day 150 cc. of whole blood was given, without reaction. On October 11 the hemoglobin was found to be at its previous level of 10.0 gm. per 100 cc. despite the 2 intervening transfusions. The urine was now rust colored but was not tested for hemoglobin. A chest film on October 12 showed clearing of parenchymal densities, with some clouding still present. The patient was discharged on October 15.

At final admission 1 month later, at the age of 15 months, the patient was moribund. He had been breathing hard and vomiting for the past three days. The temperature was 101.6°F. by rectum. A blood sample revealed a hemoglobin of 4.7 gm. per 100 cc., a white-cell count of 24,000 and a carbon dioxide combining power of 9.5 milliequiv., a potassium of 6.6 milliequiv., a sodium of 142 milliequiv. and a chloride of 114 milliequiv. per liter. Death occurred 20 minutes after admission.

At autopsy the lungs were heavy and congested, with very little air-bearing tissue. Together, they weighed 375 gm. (normal, 130 gm.). The cut surfaces were dark red and on scraping showed the typical picture of brown induration. The heart was dilated and hypertrophied, weighing 85 gm. (normal, 47 gm.). The left ventricle measured 0.8 cm., and the right ventricle 0.3 cm. at the midpoints. The liver appeared congested but was of normal weight. The bone marrow was dark red. The brain appeared edematous. The remainder of the gross autopsy was not remarkable.

Microscopical examination of the lungs showed almost all the alveoli to be filled with red cells and histiocytes, many of which contained brown pigment (Fig. 2) that stained positive for iron with Prussian blue. The alveolar walls were thickened, and the Verhoeff stain (Fig. 3) revealed patchy distribution of coarse fragmented elastic fibers. The myocardial fibers showed a diffuse fine vacuolization, which stained positive for fat. Iron stains of the liver, kidneys, spleen and pancreas were negative. The central veins of the liver were moderately dilated, but there was no evidence of chronic passive congestion. The splenic sinusoids were dilated and lined with cuboidal cells. Most of the lumens were empty, and few red cells were seen in the pulp. The malpighian corpuscles contained prominent germinal centers. The lymph-node follicles were large and also contained prominent germinal centers. The bone marrow showed marked erythroid hyperplasia. The kidneys, pancreas and adrenal glands were not remarkable on microscopical examination.

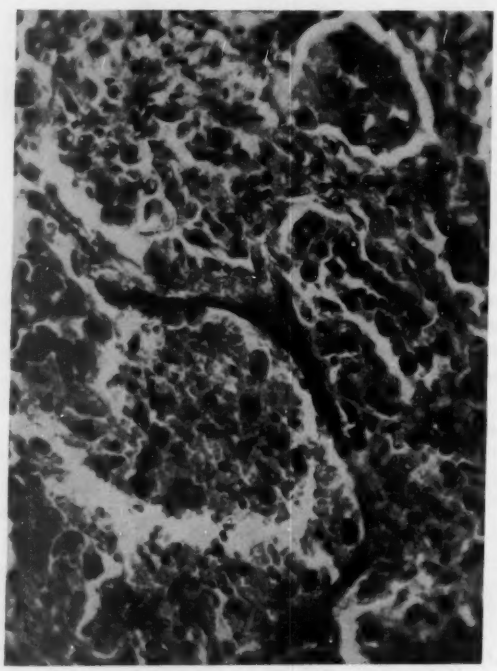

FIGURE 3. *Section of the Lung (Verhoeff's Stain X 225), Showing Coarse, Fragmented Elastic Tissue, with Many Red Cells and Histiocytes in the Alveoli.*

DISCUSSION

Idiopathic pulmonary hemosiderosis was first described by Ceelen in 1931, and in 1948 Wyllie et al.,[1]

in a survey of the literature, reviewed 17 cases, including the original report of Ceelen. To these they added 7 cases of their own. One case had been reported in a thirty-eight-year-old male, the remainder occurring between the ages of three months and sixteen years. There was no predisposition for either sex and no evidence of hereditary tendency. Since 1948 additional reports have appeared, chiefly in the European literature, and include another case in an adult.[10]

Hutchison[11] and Blachford[12] recently examined the various theories put forth to explain the pulmonary hemorrhages. The histology of the lungs has suggested a primary defect in the elastic and other supporting tissues, leading to capillary stasis and diapedesis. But similar microscopical findings have been found in brown induration associated with mitral stenosis[13]; also, abnormalities of the elastic tissue have not been a constant finding.[14] A circulatory defect, causing pressure imbalance at the capillary anastomoses between the bronchial and pulmonary arterioles in the mucosa of the terminal bronchioles, has been considered.[10] The acute exacerbations suggested the possibility of a defect in vasomotor control of the lesser circulation, resulting in periodic hemorrhage.[7] In the light of these theories it may be significant that an acute exacerbation occurred in the case reported above after transfusion when the hemoglobin was at the level of 10 gm. per 100 cc.

An allergic etiology, with the alveoli as the shock organ, was suggested by Steiner,[15] who found that splenectomy terminated the attacks in a six-year-old boy in whom the diagnosis had been established by lung biopsy.

Waldenström,[2] in an excellent clinical and radiologic discussion of the disease, posed the question of which comes first, the pulmonary hemorrhages or the iron deficiency. He reported the case of a fourteen-year-old boy first seen with a hemoglobin of 32 per cent in whom there was no sign or symptom referable to the lungs. X-ray examination was negative. The patient was placed on iron therapy, and six months later the typical pulmonary picture developed (at that time the hemoglobin was 50 per cent). In the case presented above, prematurity, maternal anemia and poor diet indicate a primary iron deficiency so that capillary damage secondary to this anemia is suggested, but there was no other evidence of a bleeding tendency.

Attention may be given primarily to the hemolytic features of the disease, which appear with considerable regularity after the initial jaundice-free episodes. Absorption of blood pigments from the lung can result in bilirubinemia and increased urobilinogen excretion, especially if there is a congested, anoxic liver. Reticulocytosis appears to follow the pulmonary hemorrhages. An autoimmune hemolytic mechanism may also contribute to the anemia. Wyllie et al.[1] noted the development of cold autoagglutinins in 5 of their cases and interpreted this as an antibody response to the red cells entrapped in the lungs. They described a patient with a cold autoagglutinin reaching the somewhat unbelievable titer of 1:10,000,000. The direct Coombs test was negative in that case and not reported in the others. A recent report, however, describes a patient in whom a positive direct Coombs test developed during an acute episode.[16]

No mention has been made of hemoglobinuria although this appears to have occurred in the case reported above during the second admission. Unfortunately, tests for cold agglutinins and hemolysins were not performed. A hemolytic element has been suggested, however, by the finding of a shortened life span of transfused erythrocytes in a five-year-old child with a severe form of the disease.[17] Unlike the patient described above, whose red cells showed increased resistance to hemolysis, fragility studies have hitherto been reported as normal, but increased resistance to hypotonic saline solution may occur in microcytic hypochromic anemia.[18]

The presence of pulmonary hemosiderosis generally indicates a poor prognosis, although Steiner's [15] recent report suggests the possible value of splenectomy in cases in which an autoimmune mechanism develops. In the series of Wyllie et al.[1] periods of remission after acute and subacute attacks varied from weeks to years, aided by good response to iron therapy; nevertheless, pallor, weakness and poor development were often present, and fine densities persisted in the chest films. In the 7 cases that they studied personally 5 patients were alive in 1948, whereas 16 of the 17 patients surveyed had died at periods varying between three months and ten years from the onset of symptoms. The liver and spleen were palpable in half these cases, and, in some, clubbing of the fingers and episodes of cyanosis developed. Death sometimes followed a severe bout of hemoptysis; however, hemoptysis was an inconstant finding and did not occur in the very young, who swallow, rather than cough up, their secretions.

It is conceivable that mild forms of the disease exist that are not diagnosed because of the few physical signs; on the other hand full-blown cases may be missed because of preoccupation with the hematologic features. The diagnosis is always suggested whenever a hemolytic picture develops in a case of microcytic hypochromic anemia. Other findings that suggest the diagnosis are persistence of fine radiologic densities in the lungs of the patient with iron-deficiency or hemolytic anemia and the presence of hemosiderin-laden histiocytes in the sputum or gastric washings.

Summary

The clinical course of a fatal case of idiopathic pulmonary hemosiderosis is presented along with the pathological findings.

The important literature is reviewed to bring out various clinical features, prognosis and theories on pathogenesis. It is suggested that this disease always be considered in the differential diagnosis of childhood anemias.

I am indebted to Lee E. Sutton, M.D., professor of pediatrics, Medical College of Virginia, for his suggestions and to the members of the Laboratory, Pathology and Pediatric staffs who contributed to the study of the patient.

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MEDICAL PROGRESS

THE HUMAN HEMOGLOBINS IN HEALTH AND DISEASE (Concluded)*

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Mixed Heterozygous Hemoglobin Diseases

Two and possibly three hemolytic diseases are now recognized that fall into the group of mixed heterozygous hemoglobin diseases. The genetic mechanism involved in the heredity of this group is schematically portrayed in Figure 12. Each patient transmits the gene for a different hemoglobin. Some of the children of such a mating will therefore be heterozygous for each of the two abnormal hemoglobins.

The most important disease in this group is sickle cell-Hgb C disease, in which the patient is heterozygous for Hgb S and Hgb C.[8,11,56,76,78,79,92,94,105,106,110,180,206,213,217] This disease was first suspected in patients with atypical sickle-cell anemia who did not fulfill all the criteria for that diagnosis. Among the atypical features were the facts that only one parent exhibited the sickling phenomenon, the spleen was usually easily palpable, in contrast to the absence of splenomegaly in adults with sickle-cell anemia, the anemia was often mild, requiring few if any transfusions, and target cells were much more prominent than in the usual case of sickle-cell anemia. Study of the hemoglobins of such patients failed to reveal the expected pattern, but showed instead a combination of Hgb S and Hgb C.[11]

Between 15 and 20 per cent of cases classified as sickle-cell anemia, re-evaluated in the light of their hemoglobin types, must now be diagnosed as sickle cell-Hgb C disease.[8,78,106] In addition a number of patients believed to have sickle-cell trait have been found to have the pattern of sickle cell-Hgb C disease. It has been estimated that the mixed heterozygous combination of Hgb S and Hgb C occurs about a third as frequently as sickle-cell anemia itself, or that approximately 1:1500 Negroes suffers from this abnormality. In this clinic 16 cases of sickle cell-Hgb C disease have been found, compared with 48 of sickle-cell anemia. Projecting these figures to the national population, it may be estimated that approximately 10,000 persons have this syndrome.

The clinical manifestations of sickle cell-Hgb C disease are striking in their variability.[8,76,106] All gradations between completely asymptomatic states to profound disability, comparable to sickle-cell anemia in severity, have been noted. Furthermore, individual cases of sickle cell-Hgb C disease manifest significant variations in symptomatology at different times, in marked contrast to the steady state of patients with sickle-cell anemia. In general, however, sickle cell-Hgb C disease is characterized by somewhat milder clinical and hematologic findings than are encountered in homozygous Hgb S disease.

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The onset of symptoms is often in early childhood, but over half the patients with sickle cell-Hgb C disease do not have difficulty until their teens or even later. Smith and Conley[8] describe a patient whose first complaint did not appear until the age of sixty-five and another who was still asymptomatic at seventy-five years of age. Fatigue, dyspnea on effort, frequent upper respiratory infections, occasional bouts of mild jaundice and arthralgia are complained of intermittently. Crises are mild and infrequent, but may at times be extremely severe and recur at close intervals. Abdominal crises are much less frequently encountered than those involving muscles and joints. Hip and low-back pain, which may be constant, is often associated with x-ray evidence of aseptic necrosis of the femoral heads, a complication that frequently occurs in this syndrome.[8,218] Hematuria and splenic infarction have also been noted in patients with sickle cell-Hgb C disease.[8,76,172,173,178] Leg ulcers, although less common than in sickle-cell anemia, have been observed in a number of cases.[219] Pregnancy appears to have a deleterious effect on the course of this disease in that clinical and hematologic crises occur in the ante-partum or post-partum period. In the series of Smith and Conley,[8] all 5 of the patients with sickle cell-Hgb C disease who became pregnant experienced exacerbations of their hemolytic disease. Two died of post-partum hemorrhage. Similar reports have been presented by Kaplan et al.[106]

Physical examination is notable in several respects. Smith and Conley[8] have pointed out that the body habitus of patients with sickle cell-Hgb C disease is normal or stocky whereas those suffering from sickle-cell anemia are usually of asthenic build. During clinically quiescent periods no physical abnormalities may be detected; during phases of active symptomatology, icterus, tachycardia, abdominal and muscle tenderness and splenomegaly are noted. Splenomegaly, absent in true sickle-cell anemia, is unique in that marked changes in the size of this organ take place, the lower pole going up or down as the symptomatology increases or decreases. Spleens not palpable at the onset of a crisis may suddenly become tender and descend 10 or more cm. below the left costal margin, only to return to their previous state after 5 or 6 days. Hepatic enlargement is infrequent.

The hematologic findings are those of a chronic, mild, normochromic, slightly microcytic hemolytic anemia (Table 6). Mean corpuscular volumes are found to vary from 65 to 90 cubic microns, with the majority about 75 cubic microns. Mean corpuscular hemoglobin concentrations are usually in the low-normal range. Normal blood counts are often obtained, and the hemolytic mechanism may only be demonstrable with difficulty. On the other hand the more severe cases show hematologic changes as marked as those seen in sickle-cell anemia. Furthermore, during periods of crises, increased hemolytic activity seems to take place, with a striking increase in the severity of the anemia. Reticulocyte counts may range from normal to extremely high levels, depending on the state of the disease, although these cells generally make up less than 10 per cent of the erythrocytes. The blood film likewise varies in its appearance with different stages of the disease. Anisocytosis and poikilocytosis are minimal, but target-cell counts range from 20 to 85 per cent, with an average of 60 per cent.[106,180] Stippling and hypochromia are not usually present. Nucleated red blood cells may be seen in large numbers, especially during periods of exacerbation. Sickling is easily elicited and may be observed on the peripheral blood film. The osmotic fragility is decreased whereas the

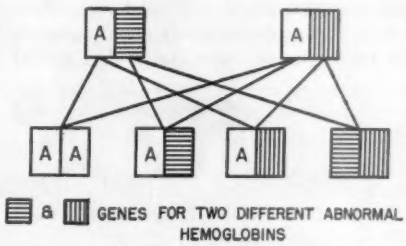

FIGURE 12. *Schematic Representation of the Hereditary Aspects of the Mixed Heterozygous Hemoglobin Diseases.*

TABLE 6. *Mixed Heterozygous Hemoglobin Diseases (Compared with Sickle-Cell Anemia).*

DISEASE	HGB TYPES	CLINICAL SEVERITY	CRISES	SEVERITY OF ANEMIA	SPLENOMEGALY	SICKLING	RED-CELL CONSTANTS	TARGET CELLS	ANISOCYTOSIS & POIKILOCYTOSIS
Sickle cell-Hgb C disease	C+S	− to +++	− to +++	− to +++	± to +++	+	Slightly microcytic normochromic	20-85% (average, 60%)	Minimal
Sickle cell-Hgb D disease	D+S	++	?	+++	− to +++	+	?	Infrequent	Marked
Sickle cell-Hgb G disease	G+S	?	++	++?	—	+	?	?	?
Sickle-cell anemia	S+S	+++	(Frequent)	+++	Absent	+	Normocytic normochromic	5-30%	Minimal

mechanical fragility is increased. Bone-marrow examinations, hemolytic-index determinations and studies of red-cell survival time all substantiate the hemolytic nature of the disease during phases of activity, but may be only slightly abnormal at other times. Hemoglobin analysis by paper electrophoresis indicates the presence of the two hemoglobins, Hgb C and Hgb S, in approximately equal amounts (Fig. 13). In the reported cases Hgb S has varied from

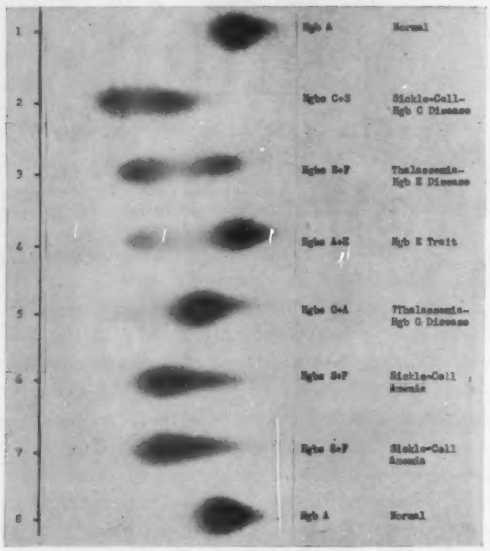

FIGURE 13. *Paper Electrophoresis of the Human Hemoglobins.*
This is an actual run of specimens from a number of miscellaneous syndromes. (Hgb G specimen provided through the courtesy of H. Schwartz.)

35 to 63 per cent, most cases falling within the range of 45 to 50 per cent Hgb S. Hgb C, present in as little as 37 per cent or as much as 60 per cent, generally comprises from 50 to 55 per cent of the total hemoglobin mass. Hgb F is occasionally increased to values of as high as 7 per cent, but in at least half the cases, normal concentrations of this pigment are found (Table 3).

Although only 3 cases of sickle cell-Hgb D disease have been described, it appears that the combination of the defects for Hgb S and Hgb D results in a moderately severe hemolytic process. The first cases, reported by Itano,[11] were in siblings described by Cooke and Mack in 1933[220] as examples of sickle-cell anemia in a white family. A third is reported as a probable case of sickle cell-Hgb D disease by Dacie.[186] Another example of this rare syndrome is alluded to without comment in an article by Schneider,[78] but no data are given and the absence of Hgb S in both parents makes the diagnosis unlikely. Insufficient data make it impossible to characterize sickle cell-Hgb D disease at present. The patients of Cooke and Mack were, at the time of the original publication, three and one-half years and fifteen months old and, when seen by Itano, twenty-two and nineteen years of age respectively. Only the history relating to their childhood is available. Splenectomy was performed in the older patient at the age of one year because of striking enlargement of this organ. The liver was also palpable at that time. No jaundice was detected. After operation the red-cell count was reported as 2,500,000, and the smear was characterized by many nucleated red blood cells, poikilocytosis, anisocytosis and polychromasia. The osmotic fragility was normal. Her brother was found to have moderate hepatomegaly with slight splenomegaly, a red-cell count of 2,500,000 (with a hemoglobin of 35 per cent), marked poikilocytosis, anisocytosis and basophilic stippling and many nucleated red cells. The osmotic fragility was normal. Sickling was present in both children and in the father, but not in the mother or other siblings.[220] Unfortunately, the recent communication by Itano[11] does not add any clinical data to those given above except for the fact that the mother and 2 of the siblings had the Hgb D trait.

The family reported by Dacie[186] consisted of a nine-year-old girl with sickle cell-Hgb D disease, 2 anisocytosis, macrocytosis, microcytosis and sickled forms. Target cells were infrequent. A few nucle- had the Hgb D trait, and another was normal. The patient was small, pale and slightly jaundiced. The liver and spleen were not palpable. The red-cell count was 2,600,000, the hemoglobin 8.4 gm. per 100 cc., the mean corpuscular volume 100 cubic microns, the mean corpuscular hemoglobin concentration 32 per cent, and the reticulocytes 9 per cent. The peripheral blood film showed marked anisocytosis, macrocytosis, microcytosis and sickled forms. Target cells were infrequent. A few nucleated red cells could be found. The osmotic fragility started at 0.55 per cent saline solution but was considerably prolonged. Because of the difficulty of distinguishing Hgb S and Hgb D except by solubility studies, no estimate of the proportion of each hemoglobin is available.[11] Furthermore, no studies of Hgb F have been carried out on these subjects.

Sickle cell-Hgb G disease was thought to be present in 2 brothers in the family reported by Schwartz and Spaet.[60,194] The older brother, twenty-eight years of age, had had a severe hemolytic anemia since the age of four, with frequent joint and abdominal crises, splenomegaly and cholecystitis. Reticulocytes were increased. The blood film revealed sickling, hypochromia, anisocytosis and target cells. The sickling test was positive. The osmotic fragility of the erythrocytes was decreased. The younger brother, twenty-six years old, with what appeared to be the same electrophoretic pattern, was completely asymptomatic except for the sickling phenomenon.

The Thalassemia Syndromes

Neal et al.[98,104,221] and others[222-228] have postulated that thalassemia major (Cooley's anemia) represents

the homozygous state for the thalassemia gene whereas the heterozygous condition results in thalassemia minor (Fig. 14). It seems unlikely that the abnormalities present in the thalassemia states are the result of a single set of alleles. There is a continuous spectrum of clinical pictures, starting with Cooley's anemia and progressing through all gradations of severity to the most asymptomatic of traits, in which the diagnosis is suggested only by minor hematologic abnormalities.[227-231] Indeed, in a number of persons, the existence of the thalassemia trait can only be inferred from the presence of a Cooley-like anemia in their offspring. These gradations in the clinical manifestations could be more easily explained on the basis of the presence of multiple interrelated genetic defects in the heterozygous or homozygous form rather than a single set of alleles. Variations in penetrance or the effect of modifiers may also be involved. From a practical standpoint, however, it is easier to consider thalassemia major (Cooley's anemia) as the homozygous form for these defects and all other diseases in this syndrome complex as heterozygous for one or more of the genetic factors involved (Fig. 14).

The basic defect in thalassemia seems to be an inability to incorporate iron into the hemoglobin molecule and perhaps an inability to form Hgb A itself.[91,105,136,221-223] However, in the present state of knowledge, it is difficult if not impossible to define with any degree of certainty what the thalassemia trait is.[232] In kinships in which one or more children with Cooley's anemia are present and both father and mother have hypochromic polycythemia, target

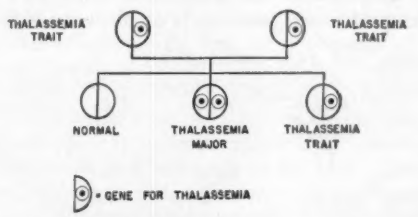

FIGURE 14. *Schematic Representation of the Hereditary Aspects of the Thalassemia Syndromes (after Valentine and Neel[221]).*

and oval cells and so forth there seems to be little doubt that the parents represent cases of the thalassemia trait. At times family studies indicate that one parent has the findings characteristic for thalassemia and the other has, at best, equivocal evidence for the diagnosis of the thalassemia defect. A number of such atypical parents can be shown to transmit the gene for an abnormal hemoglobin (Fig. 15). Still other family histories suggest the occurrence of what appears to be Cooley's anemia in the absence of any changes in the parents specific for thalassemia.[133-135] It is possible that at least some of these atypical families harbor genetic defects other than thalassemia, which in the homozygous form result in a severe hemolytic syndrome resembling Cooley's anemia. Betke[135] has referred to anemias of a similar nature in a number of patients under his observation as pseudothalassemia. Such a mechanism may explain the surprising frequency of Mediterranean anemia in some parts of the world far removed from the genetic influences of the Mediterranean races.[132,233-235] This concept receives some support from investigations carried out in Thailand on patients suffering from an anemia almost indistinguishable from Cooley's anemia.[100,132,192] In addition to the atypical family history some of these cases present two features unusual in true Cooley anemia:

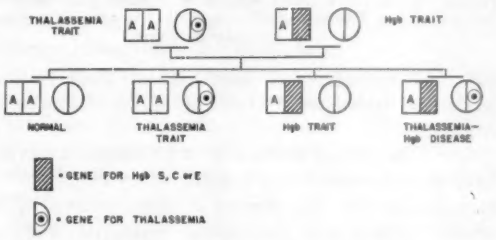

FIGURE 15. *Schematic Representation of the Genetic Aspects of the Combination of the Thalassemia Syndromes with an Abnormal Hemoglobin.*

only normal amounts of Hgb F are present [134,135]; and inclusion bodies of an undefined nature are prominent.[132-135] It is likely, furthermore, that the specific genetic defect, which results in a Cooley-like anemia in the homozygous state, when combined with the gene for Hgb E may cause the clinical picture referred to below as thalassemia-Hgb E disease. At present insufficient data are available to clarify these problems. Further study in an effort to define the defect in thalassemia is certainly indicated. To avoid undue confusion, however, all hematologic conditions resembling Cooley's anemia are referred to as thalassemia syndromes in this communication, in spite of some uncertainty about their correct classification and nomenclature.

The complex relations between thalassemia and the abnormal hemoglobins are only now undergoing extensive study. At present a number of variants of thalassemia major have been investigated. These appear to involve heterozygosity for both thalassemia and Hgb S, C or E (Fig. 15). The gene or genes responsible for thalassemia seem, almost certainly, to be located on chromosomes different from those determining Hgb A and its alleles. This concept is derived primarily from the study of kinships harboring both thalassemia and an abnormal hemoglobin by Silvestroni and Bianco[112] and by Powell et al.[111] It is theoretically possible, therefore, for a person to be homozygous or heterozygous for the thalassemia

gene and at the same time homozygous or heterozygous for an abnormal hemoglobin (Fig. 16). One can only speculate whether homozygosity for both these defects would result in a lethal combination, or in what manner homozygosity for one and heterozygosity for the other might become manifest. The variations in symptomatology that could arise under

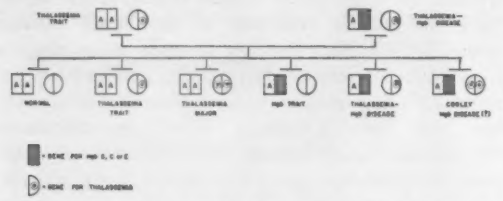

FIGURE 16. *Possible Combinations in a Mating between a Patient with a Thalassemia-Hemoglobin Disease and a Person with Thalassemia Trait.*

such circumstances may well explain some of the gradations encountered clinically in the thalassemia syndromes.

The clinical manifestations of thalassemia major have been described in a number of reviews.[222,223,225] Hematologically, this disease is characterized by a severe hypochromic microcytic hemolytic anemia with a high serum iron[236] (Table 7). Hypochromia, anisocytosis, poikilocytosis and basophilic stippling are prominent. The number of target cells is variable, but they generally comprise less than 30 to 40 per cent of the erythrocytes on the stained blood film.[106] Nucleated red cells may be numerous. Sickling is absent. The osmotic fragility is markedly decreased. The results of bone-marrow examinations and of the tests for hemolytic activity are consistent with the diagnosis of a severe hemolytic anemia.

Hemoglobin analysis indicates the presence of increased amounts of Hgb F both by electrophoresis and by alkali denaturation procedures[5,20,30,73,113,119] (Table 3). A mechanism for the increase in fetal hemoglobin has already been suggested above. No abnormal hemoglobins have been identified at present in cases of pure thalassemia major, but the suggestion has been made that newer technics may well define such abnormalities.[96] These findings may be contrasted to the hematologic data usually seen in cases of sickle-cell anemia (Table 7).

Thalassemia-Hgb S disease was first described in Italy by Silvestroni and Bianco [112,226,237-241] and is now being recognized with increasing frequency in other parts of Europe and the United States.[8,79,103,-104,111,115,242-248,248a] Patients with this disease usually inherit the thalassemia gene from one parent and the gene for Hgb S from the other (Fig. 17). Since these two abnormal factors seem to be located on different chromosomes, a parent with thalassemia-Hgb S disease may transmit either or both of these factors to his offspring (Fig. 16).

Less than 45 cases of thalassemia-Hgb S disease have been reported in the literature. Although it is premature to attempt a precise definition of its manifestations the clinical picture simulates that of

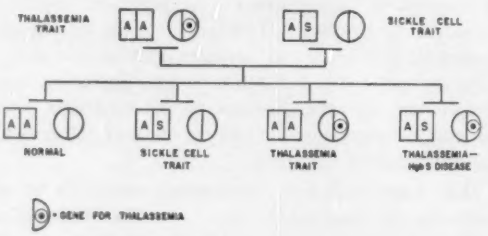

FIGURE 17. *Genetics of Thalassemia-Hemoglobin S Disease.*

Cooley's anemia but tends to be somewhat less severe. The onset of symptomatology almost always takes place before the age of ten. In addition to symptoms usually encountered in severe hemolytic anemias patients complain of frequent bone and joint pains, occasional abdominal discomfort and rare clinical crises. Jaundice is usually mild. Chronic leg ulcers, similar to those seen in sickle-cell anemia, are occasionally encountered. Patients with thalassemia-Hgb S disease are of small stature and have poor muscular development. The spleen is almost constantly enlarged although not to the degree encountered in severe thalassemia. Hepatomegaly is inconstant but may be tremendous. Aseptic necrosis of the femoral head has been reported in several cases.[246]

The hematologic findings more closely resemble those of thalassemia major than those of sickle-cell

TABLE 7. *The Thalassemia Syndromes (Compared with Sickle-Cell Anemia).*

DISEASE	SPLENOMEGALY	SEVERITY OF ANEMIA	RED-CELL CONSTANTS	ANISOCYTOSIS & POIKILOCYTOSIS	STIPPLING	TARGET CELLS	SICKLING
						%	
Thalassemia major	++++	++++	Microcytic hypochromic	+++	++	10-35	–
Thalassemia-Hgb S disease	++	+++	Microcytic hypochromic	+++	++	20-40	+
Thalassemia-Hgb C disease	?	(?) — to ++	Microcytic hypochromic (?)	++	+	(Increased)	–
Thalassemia-Hgb E disease	++++	++++	Microcytic hypochromic	+++	++	10-40	–
Sickle-cell anemia	Absent	+++	Normocytic normochromic	±	–	5-30	+

anemia (Table 7). Anemia is moderately severe and relatively constant. Erythrocyte counts fall within the range of 2,500,000 to 4,000,000, averaging approximately 3,000,000. Hemoglobin values vary from 6 to 9 gm. per 100 cc. The red-cell constants define a hypochromic, microcytic anemia with mean corpuscular volumes from 65 to 80 cubic microns and mean corpuscular hemoglobin concentrations from 22 to 30 per cent. Reticulocyte counts are moderately elevated. On the stained blood film hypochromia, microcytosis, anisocytosis, poikilocytosis, ovalocytosis, basophilic stippling and polychromasia are prominent. Target cells vary from 20 to 40 per cent. Occasional sickled erythrocytes are present on the blood film, and sickling may be easily elicited. Normoblasts are usually strikingly increased, as many as 200 to 300 per 100 white blood cells being seen. As in thalassemia the osmotic fragility is decreased. Determinations of hemolytic index and red-cell life span support the diagnosis of a moderately severe hemolytic process.

Hemoglobin analysis reveals the presence of a complex mixture of pigments. Except for the case reported by Humble and his associates[247] Hgb S has comprised 60 to 88 per cent of the total hemoglobin.[8,79,103,104,243,244] The amount of Hgb F may vary from normal to 20 per cent, but has usually been only moderately elevated. Hgb A is also present in concentrations of up to approximately 20 per cent. The observations of Humble et al.[247] are incomplete, and their report of almost 100 per cent Hgb S in this syndrome must be re-examined (Table 3).

Thalassemia-Hgb S disease may be differentiated from Cooley's anemia by the presence of sickling on the blood film and a hemoglobin formula of Hgb S + Hgb F + Hgb A. It may be distinguished from sickle-cell anemia by the low mean corpuscular volume and mean corpuscular hemoglobin concentration and the characteristic morphologic changes on the stained blood film. Description of the hematologic and clinical findings in patients homozygous for thalassemia and heterozygous for Hgb S has not yet been published, although Silvestroni and Bianco[112] may have observed 2 such cases.

The diagnosis of thalassemia-Hgb C disease has been made in only 3 patients. The reported descriptions are so different that there seems little point in reviewing these findings extensively. In the 2 cases of Singer et al.[105] 74 per cent and 77 per cent Hgb C were found in combination with Hgb A. This formula, Hgb C + Hgb A, is comparable to the pattern of Hgb S + Hgb A seen in thalassemia-Hgb S disease, in which Hgb S forms 60 to 80 per cent of the total pigment. In a report by Zuelzer and Kaplan[249] the hemoglobin concentrations found were comparable to those seen in Hgb C trait—that is, 71 per cent Hgb A and 29 per cent Hgb C. The 2 patients of Singer et al. were only slightly anemic, and the patient of Zuelzer and Kaplan moderately so. Both report microcytosis but differ concerning hypochromia. Target cells were increased in all 3 patients. Obviously, further studies of this syndrome will be necessary to evaluate these diverse findings.

Thalassemia-Hgb E disease is a severe hemolytic syndrome that closely mimics Cooley's anemia in its manifestations.[57,58] In all cases studied one parent has been found to have Hgb E and the other what appears to be, at best, very mild thalassemia.[58,100,192] Whether the parents without Hgb E really have thalassemia minor and whether this syndrome is correctly named are problems that have already been alluded to.

The clinical findings in thalassemia-Hgb E disease and thalassemia major are indistinguishable except for minor features.[109,188,192] Thalassemia-Hgb E disease usually has its onset in infancy although an occasional patient will not seek medical attention until his teens or later. Most of the latter group, however, have been in poor health for as long as they could remember. Symptoms of increasing weight loss, retarded development, fatigue, dyspnea on effort, arthralgias, pallor and jaundice are frequent. The abdomen becomes protuberant and leads to mechanical difficulties in eating and maintaining an erect posture.

Examination of children with thalassemia-Hgb E disease reveals a huge, protuberant abdomen to which are attached four matchsticklike extremities. Mongoloid features are not striking. The hair is sparse and often almost absent. Jaundice is marked. Splenomegaly is a constant feature, the enlarged organ often extending into the pelvis. Hepatomegaly is moderate but not always present. Secondary sexual characteristics are lacking.

Hematologic investigation reveals a microcytic, hypochromic, hemolytic anemia with the red-cell count and hemoglobin level usually as low as in the most severe examples of Cooley's anemia (Table 7). The corpuscular constants are as expected. Reticulocyte counts are moderately elevated. Cellular morphology on the stained blood film is identical with that found in Cooley's anemia except that in some patients up to 8 per cent or 10 per cent of the erythrocytes resemble spherocytes (Fig. 8). The occurrence of spherocytosis may explain the observation that hemolysis starts in saline solutions more concentrated than in the normal person (Fig. 9). Complete hemolysis does not occur until a concentration of 0.12 per cent saline solution or less has been reached.[109,192] Nucleated red blood cells are prominent with as high as 200 to 300 nucleated red blood cells per 100 white blood cells. Bone-marrow examination shows marked erythrocytic hyperplasia. Survival-time studies by the chromium-51 technic indicate a shortened red-cell life span.[193] The hemolytic index is elevated.

Hemoglobin analysis in patients who have received no transfusions for a suitable period have shown a mixture of Hgb E plus Hgb F, the latter pigment comprising 20 to 40 per cent of the total [57,58,109,192]

(Table 3). After transfusions variable quantities of Hgb A may also be found.

Two patients with what was believed to be thalassemia-Hgb G disease were observed in the large family studied by Schwartz and Spaet.[60] The erythrocyte morphology was abnormal in that hypochromia, anisocytosis, occasional stippled cells and target cells were present. Anemia was moderate in degree and the reticulocyte counts were approximately 2.5 per cent. Cr^{51} studies of survival time showed a decreased life span for the erythrocytes. Except for an increased osmotic resistance of the erythrocytes, no further data were available. Hgb F has not been found in abnormal concentrations.[194]

The combination of hereditary spherocytosis and Hgb S has been reported by Smith and Conley[6] in one patient. It is anticipated that other genetic defects of the red cells will be found in association with the abnormal hemoglobins. Descriptions of such mixed heterozygous syndromes will be eagerly awaited.

Sickle-Cell Anemia in the White Race

Many observers now consider Negro ancestry a *sine qua non* for the presence of the sickling phenomenon no matter how remote the admixture or how minimal the Negroid characteristics. It is therefore no longer of great moment to describe cases of sickle-cell anemia in the white race. Nevertheless, in the forty-five years since Herrick's[250] original description of sickle-cell anemia, approximately 30 reports have appeared in the literature describing the occurrence of this disease in Caucasians.[147,148,220,251-277] Many of the early cases can be excluded because of misdiagnosis of what was, at that time, an ill defined syndrome. Some 20 cases, however, have been accepted as true sickle-cell anemia in the white race. Re-examination of some of these patients in the light of present-day knowledge has made it possible to reclassify a number of these cases, and the correct diagnosis may be suspected from a review of the published reports in others.

If one accepts the genetic criteria that a patient with sickle-cell anemia is homozygous for Hgb S and must therefore have inherited a gene for this abnormal hemoglobin from each parent, only 1 case, the second patient in the report of Morrison et al.,[268] fulfills the requirements for this diagnosis. The hematologic data presented are consistent with the findings seen in sickle-cell anemia, although a precise description of the blood findings is not included. In view of the prevalence of the sickling phenomenon among the peoples of the Mediterranean area, it is not surprising to find sickle-cell anemia in a child of "white" Italian ancestry. The patient of Guyton and Heinle,[272] a nineteen-year-old Sicilian female, may also have had sickle-cell anemia although only her mother was available for study. In all other reported cases sickling is absent in one or both parents, excluding, except for possible technical difficulties, the diagnosis of sickle-cell anemia. In addition, when data sufficient for evaluation are included, it may be stated that not one of these persons has a hematologic pattern consistent with true sickle-cell anemia. All these reports must therefore be considered as describing other diseases, in most cases one of the sickle-cell variants.

In several cases, the exact diagnosis has been established by restudy of the patient. Thus, the 2 patients of Cooke and Mack,[220] described in 1934, are now known to have had sickle cell-Hgb D disease.[11] The cases of Haden and Evans[261] have been shown to be examples of thalassemia-Hgb S disease,[245] and that of Shotten et al.,[276] sickle cell-Hgb C disease.[278]

The remaining reports may be divided into those with a probable diagnosis of a specific hemolytic anemia and those with data insufficient to justify any conclusion. Ten reports comprising 14 patients fit the pattern described for thalassemia-Hgb S disease.[147,254,256,261,263-265,270,271,277] All patients were of Greek or Italian extraction except for a single patient, one of whose parents was from Spain and the other from New Orleans (reported as Case 1 by Ogden[147]). Two additional cases, those of Sights and Simon[255] and Stewart,[253] may be examples of this syndrome, but insufficient information is presented for a critical evaluation. The fact that the patient of Sights and Simon was of Irish, and the patient of Stewart of Cuban and English descent may cast some doubt on this diagnosis.

Two reports appear to be of cases of sickle cell-Hgb C disease. These are the thirteen-year-old Egyptian girl described by Abbasy[273] and the twenty-six-year-old man of Greek extraction presented by Gordon and Gardner.[275] Unfortunately, the latter authors did not describe the blood film so that the diagnosis may have been in error. Two other reports suggest the diagnosis, but so little pertinent information is given as to make this a mere guess. These are Case 2 of Ogden[147] and the patient of Caccamo and Strutner.[274]

The remaining descriptions either are so inadequate that no specific suggestions can be made[251,260,262,266-268] or are concerned with disease other than sickle-cell anemia or its variants. Pollock and Dameshek[258] and Lawrence[252] dealt with elliptocytosis, as Lawrence[279] later recognized. Both the parents of Clarke's[257] patients were nonsicklers, and the hematologic description does not fit that of sickle-cell anemia. The 3 cases of Wallace and Killingsworth[259] probably had sickle-cell trait. The subject of a report by Greenwald et al.[269] most probably had sickle-cell trait with an acquired hemolytic anemia secondary to carcinomatosis.

Reports of sickle-cell anemia in Caucasians no longer arouse the interest once shown by such communications. As noted above, only 1 and possibly a second case can be accepted as true sickle-cell anemia. Most of the others are examples of thalasse-

mia-Hgb S disease among Mediterranean people, in whom ample opportunity for admixture of the two genes exists. A rare case of sickle cell-Hgb C disease may masquerade as sickle-cell anemia in the white race, but this is most unusual since both Hgb S and Hgb C are characteristics of dark-skinned races. Since both defects are found in Africa one may expect an occasional report of sickle cell-Hgb C disease from this region. I am therefore inclined to agree with Plachta and Speer[148] and with Ogden[147] that sickling is strong evidence for admixture with Negro blood and that the occurrence of sickle-cell anemia in the white race can be adequately explained by careful study of the patient and his family.

Conclusions

This review has summarized the important biochemical aspects of the eight human hemoglobin types now recognized and has outlined the clinical and hematologic features of the many syndromes resulting from their action. At present insufficient data are available for one to be dogmatic about the findings in a number of these diseases. Furthermore, many problems exist about which one can only speculate at present. Notable among these are the questions related to the genetics of the hemoglobins and the nature of the thalassemia syndromes. It is hoped that further study may elucidate some of these mysteries.

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MEDICAL INTELLIGENCE

IODIPAMIDE (CHOLOGRAFIN) ADMINISTRATION*

Its Effect on the Thyroid Uptake of I^{131} and the Serum Precipitable Iodine in Euthyroid Persons

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AFTER the administration of iodine-containing x-ray contrast mediums, such as iodoalphionic acid (Priodax), iodopyracet (Diodrast) and iodinated oil (Lipiodol), a decrease in the thyroid uptake of radioactive iodine (I^{131}) and an increase in the serum precipitable iodine occur. These effects are considered to be a result of the liberation of iodide from these organic molecules.[1] In a recently developed x-ray contrast medium, iodipamide (Cholografin, disodium N, N'-adipyl-bis [3-amino-2,4,6,-triiodo] benzoic acid),§ the iodine content was found to remain firmly bound in the molecule after its intravenous injection.[2] This observation suggested that this medium might not alter the thyroid uptake of I^{131}. Since iodipamide is becoming more widely used roentgenologically[3,4] the following study was undertaken to determine whether its administration would affect these two important clinical tests of thyroid function.

METHOD

Seven euthyroid patients having routine intravenous cholangiography were studied. Before cholangiography, thyroid status was evaluated by clinical examination, by I^{131} uptake and, in most cases, by determination of serum precipitable iodine. Iodide (organic or inorganic) had not been administered to any of the 7 patients during the previous ten months. Six of them had undergone cholecystectomy for cholelithiasis. Liver function was normal clinically and by appropriate laboratory tests in 4 of these 6 patients. The seventh (D.P.) had portal cirrhosis, with moderate hepatomegaly, esophageal varices and moderately abnormal liver-function tests. Of the remaining 2, T.M. had slight hepatomegaly and slight impairment of liver function and H.G. had moderate bromthaleinsulfonate retention. Kidney function in all was normal clinically, by complete clinical urinalysis and, when done, by determination of blood nonprotein nitrogen.

Forty to sixty cubic centimeters of a 20 per cent aqueous solution of iodipamide was administered intravenously to each patient; in 5, adequate roentgenographic visualization of the biliary tract resulted. One of the remaining 2 patients received a second and larger dose, with adequate visualization. Subsequently, at varying intervals, the twenty-four-hour thyroid uptake of I^{131} was determined by the method of Freedberg et al. (euthyroid average, 29 per cent ± standard deviation of 5 per cent).[5] The serum precipitable iodine was measured by a modification of the method of Barker and Soley[6] or, occasionally, by the method of Zak et al.[7] (euthyroid range, 4 to 8 microgm. per 100 cc.). In several cases the total serum iodide was measured. During the period of study all patients avoided contact with iodine-rich substances.

RESULTS

The results are given in Table 1. A marked decrease in I^{131} uptake was observed regularly within the first two to seven days after iodipamide administration; during this period, the serum precipitable iodine was increased regularly far above the maximum determinable value by the method used (50 microgm. per 100 cc.). Thereafter the results of these two tests gradually returned to normal control levels. The I^{131} uptake was at the control level in 3 patients in fifty-nine, one hundred and seven and one hundred and fifty-nine days, respectively; in a fourth patient it was near the control level at fifty-four days. The serum precipitable iodine had returned to the control level in 1 patient at one hundred and seven days, and in the others it was decreasing; when last determined at thirty-six to sixty-six days, however, it remained two to four times the normal levels. Serum inorganic iodide was determined in 5 patients at thirty-six to one hundred and seven days, disclosing in each a normal result of 1.2 to 2.8 microgm. per 100 cc., averaging 1.8 microgm.

DISCUSSION

A regular decrease of the thyroid uptake of I^{131} and an increase of the serum precipitable iodine after iodipamide cholangiography have been demonstrated in 7 patients. The onset of these effects occurred within twenty-four hours, and the duration extended beyond two months, appearing to average about three months in this small group of euthyroid subjects.

The duration of these effects is probably determined by several factors. One, the rate of iodipamide excretion, has not been thoroughly studied in man; in dogs 21 per cent of 60 mg. per kilogram of body

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§Iodipamide used in this study was kindly supplied as Cholografin by the E. R. Squibb Company, New York City.

weight given intravenously was excreted in six hours, mostly in bile.[2] Other doubtlessly important factors, such as dose size and the status of liver and kidney function, could not be well correlated with the results in the present study.

The mechanism altering these tests of thyroid function after the administration of iodoalphionic acid and of other x-ray diagnostic mediums has been shown to result from iodide liberation from their organic molecules.[8,9] The iodine linkage in iodipamide is stronger by virtue of the protective property of -COONa radicles located ortho and para to the iodine atoms; and the in vivo liberation of iodide in urine could not be demonstrated in man or animal by a chloroform extraction and iodate conversion method, sensitive to 0.1 part per 1000 of the dose used.[10] However, a quantity of iodide small enough to escape detection by this method — for example, 0.5 mg. a day — is large enough to decrease I^{131} uptake markedly.[11] Iodipamide is unstable in light, and after prolonged exposure it catalyzes the reaction of ceric sulfate and arsenious acid, suggesting iodide liberation.* An intact iodipamide molecule per se, being readily adsorbed to plasma protein,[2] would increase the serum precipitable iodine, but, consisting only of organic iodide, it is not concentrated by the thyroid gland[10] and therefore should not directly affect the I^{131} uptake. Iodipamide inhibition of thyroid-stimulating hormone, with a resulting decrease in I^{131} uptake, is a theoretical possibility.

Our results, therefore, indicate the retention in the body of serum protein-bound iodipamide, which directly increases the serum precipitable iodine and indirectly, through liberation of small quantities of iodide, decreases the thyroid I^{131} uptake.

*These tests were performed by Dr. Milton W. Hamolsky.

Summary and Conclusions

Intravenous iodipamide administration in euthyroid persons decreased significantly thyroid uptake of I^{131} and increased serum precipitable iodine regularly for longer than two months and for an average of about three months.

Iodipamide is to be added to the list of iodide-liberating substances whose effects must be considered in the interpretation of I^{131} tests of thyroid function and determinations of serum precipitable iodine.

We are indebted to Dr. A. Stone Freedberg and Dr. Felix G. Fleischner for their help in this study.

Table 1. *Effect of Iodipamide Administration on the Twenty-Four-Hour Thyroid Uptake of I^{131} and on Serum Precipitable Iodine.*

Patient	Age	Sex	Race	Control		After Iodipamide (Interval in Days)				
				I^{131} uptake	Serum iodine	I^{131} uptake	Interval	Serum iodine	Interval	Diagnosis
				%	*microgm./100 cc.*	%	*days*	*microgm./100 cc.*	*days*	
T.M.	45	M	W	26	—	7 23	3 159	—	—	Diabetes mellitus & chronic pancreatitis
J.L.	70	M	N	47	—	20	3	>50.0	1	Subhepatic abscess
A.N.	59	F	W	31	7.3	9 29	2 107	>50.0 7.8 10.2*	1 107	Biliary dyskinesia?
D.P.	68	M	W	42	5.2	10 23	5 29	>50.0 >20.0 21.8 23.2*	8 28 66	Portal cirrhosis
S.B.	49	F	W	17	—	11 11 16	4 9 59	>50.0 >50.0 14 16.8*	4 9 59	Pulmonary emboli
H.G.	69	M	W	25	5.7	10 16	7 36	18.2 19.6*	36	Angina pectoris & duodenal ulcer
H.J.	61	F	W	22	5.2	18	54	9.6 10.8*	53	Spasm of sphincter of Oddi due to codeine sensitivity

*Total serum iodine.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41361

PRESENTATION OF CASE

First admission. A forty-six-year-old medical secretary entered the hospital complaining of fever.

Six months before admission she was awakened by a severe paroxysm of coughing that lasted about three minutes. No sputum was raised, and there was no associated pain or fever. One month later she had a brief shaking chill. Shortly thereafter, she began to feel tired and "run down." A physician told her he was unable to find anything wrong with her. He prescribed penicillin by mouth. Her appetite became poor, and she began to have chills and chilly sensations from time to time. Four months before entry she took her temperature for the first time and noticed that it was rising in the afternoon and was reaching 102 to 104°F. in the evening. The fever was intermittent, receding two or three days after an injection of penicillin, which she received once a week, and recurring two to four days later. She was now very fatigued and gave up her job. Fever and anorexia continued, and she had lost about 6 to 12 pounds in weight. A week before admission there was a recurrence of paroxysms of coughing accompanied by choking sensations, nausea and vomiting. The cough was unproductive and was not accompanied by pleuritic pain. The patient had never been to the tropics. She was not sure whether or not she had drunk raw milk during a vacation in New Hampshire six months before admission. She had 2 cats and 3 dogs, but was not aware of having been scratched.

The family history was noncontributory.

Physical examination revealed a thin, flushed woman who appeared chronically ill. The teeth were in rather poor condition. The lungs were clear to percussion and auscultation. The heart was not enlarged. There was a Grade 1 systolic murmur at the apex. One observer palpated the liver edge 1 or 2 cm. below the right costal margin on deep inspiration. The spleen was not felt. There was no abdominal or costovertebral-angle tenderness. A few nontender lymph nodes, 1 or 2 cm. in diameter, were palpated in the axillas and the right side of the neck. There were no petechiae or splinter hemorrhages. Clubbing was absent.

The temperature was 102.6°F., the pulse 112, and the respirations 20. The blood pressure was 112 systolic, 70 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 11 gm. per 100 cc. and a white-cell count of 6200, with 70 per cent neutrophils, 15 per cent lymphocytes, 6 per cent monocytes, 8 per cent eosinophils and 1 per cent basophils; in a subsequent differential count there was only 1 per cent eosinophils. Slight hypochromia, polychromasia, anisocytosis and some microcytosis of red cells were noted on smear. The sedimentation rate was 60 mm. per hour uncorrected and 22 mm. corrected. The sodium was 127 milliequiv., and the chloride 92 milliequiv. per liter; the total protein was 6.9 gm., the albumin 3.3 gm., and the globulin 3.6 gm. per 100 cc. The nonprotein nitrogen, calcium, phosphorus, uric acid, potassium and phosphatase were normal. Cephalin flocculation was ++ after both twenty-four and forty-eight hours. The electrophoretic pattern of the serum showed a high alpha-2 globulin. A Widal test and an agglutination test for brucella were negative. There was no growth in bacteriologic cultures of blood. The blood Hinton test was negative. Skin tests with PPD (precipitated protein derivative) tuberculin were negative in first and second strengths after twenty-four and forty-eight hours. X-ray films and fluoroscopy of the chest showed an ill defined fullness in the paratracheal, carinal and hilar regions suggestive of lymphadenopathy (Fig. 1). The lungs showed thin areas of strandlike increased density. Barium-swallow examination was unremarkable. An intravenous pyelogram revealed prompt dye excretion. The calyxes were not blunted. The right-psoas-muscle shadow was not well outlined, and the upper ureter was displaced laterally. A film of the paranasal sinuses was normal. X-ray examination of the bones gave no evidence of metastases. A lymph-node biopsy was refused by the patient.

The temperature spiked daily to 101 to 104°F., reaching its height in the late evening or early morning. The patient was discharged against advice on the seventh hospital day.

Final admission (five months later). After discharge fever and sensations of chilliness continued for a month or so, but were less in evidence thereafter. The patient began to feel generally better although she was weak and short of breath on exertion. Her appetite continued to be poor, and she lost an additional estimated 15 pounds in weight.

She occasionally coughed and raised a small amount of white sputum. Five days before entry she suddenly experienced a shaking chill, with chattering of the teeth. Her temperature after this episode was 104°F. At 3 p.m. on the day before admission, while lying in bed, she was suddenly seized with a sharp pain in the lower abdomen that reminded her of a labor pain. It radiated to the epigastrium and back. There was no associated nausea, vomiting or change in bowel habits. Demerol produced considerable relief, the pain disappearing by the morning of admission. The temperature spiked to 105°F. on the evening before admission.

On admission the patient appeared acutely ill, with evidence of weight loss. The heart was unchanged from the previous examination. A few sticky rales and rhonchi were heard over the right lower portion of the chest. The liver was palpable 2 fingerbreadths below the right costal margin on deep inspiration. No other masses were felt in the abdomen. A few discrete lymph nodes, 1 or 2 cm. in diameter, were noted in the right side of the neck, axillas and groins.

The temperature was 104°F., the pulse 108, and the respirations 24. The blood pressure was 90 systolic, 50 diastolic.

Urinalysis was unremarkable except for a ++ test for albumin and occasional granular casts and 1 to 3 red cells and white cells per high-power field in the sediment. Examination of the blood revealed a white-cell count of 6500, with 74 per cent neutrophils, 16 per cent band forms, 6 per cent metamyelocytes, 2 per cent lymphocytes, 1 per cent monocytes and 1 per cent eosinophils. The hemoglobin was 7.9 gm. per 100 cc. The red cells on smear showed moderate hypochromia, anisocytosis and poikilocytosis. The corrected sedimentation rate was 10 mm. per hour. A Coombs test was negative. The total protein was 6.2 gm., the albumin 3.5 gm., the globulin 2.7 gm., the fasting blood sugar 115 mg., the alkaline phosphatase 14.8 units, the bilirubin 0.7 mg., the calcium 8.9 mg. (Fiske method) and 7.2 mg. (EDTA), and phosphorus 1.8 mg. per 100 cc.; the sodium was 119 milliequiv., and the chloride 83 milliequiv. per liter; the potassium, nonprotein nitrogen and carbon dioxide were normal. The prothrombin time was 25 per cent; cephalin flocculation was +++ in twenty-four and forty-eight hours, and the bromsulfalein test showed 29 per cent retention of the dye. A bone-marrow smear was interpreted as normal except for an excess of neutrophils (26 per cent) with a myeloid-erythroid ratio of 5:1. A blood Hinton test was negative. Cerebrospinal fluid was unremarkable except for a sugar of 93 mg. per 100 cc. Brucella, Widal and heterophil-antibody agglutination tests were negative. Throat culture grew alpha-hemolytic streptococcus, *Staphylococcus albus* and coliform bacteria. Urine culture grew *Escherichia coli, Staph. albus* and rare coliform bacteria. Two stool specimens gave a negative guaiac test. An x-ray film of the chest gave no definite evidence of hilar or mediastinal adenopathy. The lungs were clear. The spleen was not enlarged. A plain film of the abdomen was not remarkable. An intravenous pyelogram was unsatisfactory, but there was no evidence of a retroperitoneal mass.

The patient ran an irregularly febrile course, her temperature often rising above 104°F. Her condition progressively worsened; from time to time she was disoriented or having hallucinations. With transfusions and supportive therapy the hemoglobin rose to 12 gm. per 100 cc., and the electrolytes approached normal. However, the nonprotein nitrogen rose steadily to 139 mg. per 100 cc. on the eleventh hospital day, when she went into shock. There were coarse expiratory rales and dullness over the right side of the chest, and the abdomen was distended. She regurgitated a few cubic centimeters of bloody material, and died shortly thereafter.

FIGURE 1. *Roentgenogram of the Chest, Showing Minimal Paratracheal and Bilateral Hilar Adenopathy on the Right.*

DIFFERENTIAL DIAGNOSIS

DR. JOHN W. KELLER*: I do not know what the occupational hazards of this particular medical secretary were, but I do know that she was in the age group for tumor.

May I see the x-ray films now?

DR. JOSEPH HANELIN: I should agree with the interpretation of the x-ray films of the chest. There is a suggestion of minimal adenopathy in the hilar areas as well as in the right paratracheal region (Fig. 1). A pyelogram done during this admission shows good renal function. I am not entirely convinced

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about the ureteral displacement in the pyelograms, nor can I define any abnormal masses in the abdomen. The right ureter is described in the protocol as being displaced laterally. If anything, it looks as though it may be displaced medially, but there is considerable normal variation in the course of the ureter and this may not be an important finding. The liver and spleen are about normal in size; even though the liver edge was palpable, from the film I cannot be sure of any hepatic enlargement. I think we are much more reliable in the evaluation of the size of the spleen than we are of the size of the liver.

Six months later another chest examination shows little change except for more feathering of the bronchial markings. The evidence for adenopathy is no greater than before — perhaps less. The pyelograms on the final admission were not successful although there is now indication of bilateral functional renal impairment. The liver is somewhat fuller than it was; the spleen has not obviously increased in size.

DR. KELLER: Is there any suggestion of histoplasmosis in the lungs?

DR. HANELIN: No; I do not see any suggestion of it.

DR. KELLER: I gather from what you say that the lungs at the final admission do not show improvement from the previous x-ray films — is that right?

DR. HANELIN: They are much the same.

DR. KELLER: That is different from what the protocol says — it says that the x-ray films taken during the second admission were normal.

First of all, I should like to talk about the first admission. The patient did not have a chronic cough, but a paroxysmal cough, which I think was due to irritation or to an obstructive phenomenon rather than to tuberculosis or widespread lung infection. The cough occurred six months before the first admission at about the time that she had drunk unpasteurized milk. I think it is safe to say that a person who goes to New Hampshire and is forty-six years old has probably ingested unpasteurized milk in the past. It was offered to me within the past five days, and it is delicious. Certainly, she may have ingested some brucella organisms, but if she had I think she would have been much sicker more rapidly. Brucellosis can have a protracted course, but does not present this picture.

Five months before admission she had a shaking chill, which suggests a bacteremia, but I have no proof of that. A month later she took her temperature and discovered that although she felt moderately well, — actually she felt run down, — she had a fever. That indicates to me that she was surprised about the elevated temperature. This waxing and waning fever suggests the Pel–Ebstein fever of Hodgkin's disease. I think that she connected the subsidence of it with the injections of penicillin because she was trying to give her physician credit for the improvement. Patients sometimes want the therapy to be effective, and give credit where credit is not due.

The comment about the menagerie at home is an interesting sidelight into the life of a medical secretary. There was no mention of any breaks in the skin from the cats. I do not think that she had cat-scratch fever.

I am not given a description of the enlarged lymph nodes. Were they hard or rubbery? Was there anything distinctive about them?

DR. WINFIELD S. MORGAN: They were described as small, firm, nontender and freely movable.

DR. KELLER: The reversed albumin-globulin ratio interests me, although later it was normal. It suggests sarcoidosis, lymphogranuloma venereum and severe liver disease. Although the liver was slightly enlarged — I believe the first observer was accurate, for later it became larger — the liver-function studies did not indicate that she had liver disease in the beginning. The cephalin flocculation was within normal limits on the first admission. About the high alpha-2 globulin, there is a report of a series of 10 patients with Hodgkin's disease,* 70 per cent of whom had an increase in the alpha-2 fraction of the globulin to over 1.0 gm. per 100 cc. Of those with other lymphomatous diseases, 27 per cent had an elevation of the alpha-2 fraction to over 1.0 gm. per 100 cc.

There was conflicting evidence of exposure to tuberculosis — she was a medical secretary and she may or may not have drunk raw milk. I can accept the tuberculin skin tests or I can doubt them. If the test with purified protein derivative was negative in those two strengths and if the derivative was properly prepared and fresh I should choose to accept them. However, I shall accept the agglutination tests — the Widal and the brucella — as well as the blood Hinton test.

The increased percentage of eosinophils could be a lead to a parasitic disease or Hodgkin's lymphoma. I am inclined to discount that, for it was elevated on only one of three counts.

The patient was discharged, to return five months later because of a sharp pain in the lower part of the abdomen that reminded her of a labor pain. I do not know what that was. I suppose a low-salt syndrome could have been the source of it, but I think it is unlikely. The urine on admission showed changes, but they were entirely consistent with the illness and the fever. The low hemoglobin suggested to her physicians a hemolytic anemia, but the Coombs test was negative. The fact that the globulin had returned to normal levels makes me wonder if it had been elevated previously on the basis of an extensive

*Arends, T., Coonrad, E. V., and Rundles, R. W. Serum proteins in Hodgkin's disease and malignant lymphoma. *Am. J. Med.* 16:833-841, 1954.

infection. There was an elevation of the cerebrospinal-fluid sugar. If the lumbar puncture was done at the time that the nonprotein nitrogen was elevated, I could attribute the rise in the sugar to uremia.

During this final episode, which began after about eleven months of illness, she showed an increase in the size of the liver and an increase in the number of enlarged lymph nodes, with the addition of enlarged lymph nodes in the groin. The radiologists were not helpful in demonstrating enlarged lymph nodes; nevertheless, the physical examination revealed them. She vomited 2 cc. of bloody material, as the result of uremic gastritis, I believe, rather than of loss of blood into the gastrointestinal tract.

The big question to resolve is whether she had had an infection or a tumor for all these months. Among the possibilities is sarcoidosis, with the reversal of the albumin-globulin ratio, but I think that there was no good evidence of that in either the clinical or the laboratory picture. She had never had any enlargement of the spleen, and the calcium had been normal at all times. The possibility of amyloidosis exists, but primary amyloidosis is a long shot. I do not think that she had been ill long enough for secondary amyloidosis to have been present. Moreover, that would not have explained the reversal of the albumin-globulin ratio. There is a fair possibility that she had histoplasmosis. No histoplasmin skin test was reported. I suspect that none was done.

I should favor a malignant lymphoma as the cause of death. I think a person who had been ill at least a couple of months but had continued to work in spite of an elevated temperature, and had continued to lose weight and had lymphadenopathy, fits the picture of lymphoma.

DR. JOHN T. QUINBY: I wondered if the renal involvement could be explained on the basis of a malignant process.

DR. KELLER: When you say renal involvement, do you mean that the nonprotein nitrogen rose terminally, or are you referring to the displacement of the ureter?

DR. QUINBY: Albuminuria was present.

DR. KELLER: I should be willing to explain that amount of urinary albumin on the debility of the patient and the chronic fever. If there had been more casts, or more red cells or other abnormalities, I should consider renal involvement.

DR. ALLAN L. FRIEDLICH: This patient was on our service. We reached the same conclusion that Dr. Keller did, and we were distressed that she did not have a chance to receive the benefit of therapy. At the time of the final admission we were anxious to do a biopsy to establish the diagnosis, but she was too sick to tolerate the procedure. If we have anything to learn from this case it is that it is sometimes hazardous to discharge a patient against advice.

CLINICAL DIAGNOSIS

Fever of unknown origin.
?Malignant lymphoma.

DR. JOHN W. KELLER'S DIAGNOSIS

Malignant lymphoma.

ANATOMICAL DIAGNOSIS

Malignant lymphoma, Hodgkin's type, involving lymph nodes, spleen and bone marrow.

PATHOLOGICAL DISCUSSION

DR. MORGAN: At autopsy the striking abnormal finding was the generalized lymphadenopathy, which was most prominent in the para-aortic, the mesenteric and the mediastinal regions, where the lymph nodes were soft, discrete and measured 2 to 4 cm. in greatest dimension. The spleen was several times the normal size, weighing about 500 gm. On section this did not show any loss of the follicular architecture, but all the follicles were considerably increased in size. The bone marrow of the femur and spine was firm and white. The liver and kidneys were somewhat heavy but microscopically showed only nonspecific degenerative changes that we would attribute to toxemia. The lungs showed a moderate amount of congestion and edema. Microscopically, the lymph nodes, the follicular areas of the spleen and the bone marrow were either partially or completely replaced by a pleomorphic cellular infiltration of the lymphoid series, scattered throughout which were moderate numbers of Reed–Sternberg cells, eosinophils and areas of necrosis. These constitute the microscopical picture of malignant lymphoma, Hodgkin's type. I believe that much of this patient's fever could be attributed to the necrosis in lymph nodes, which was prominent.

DR. HANELIN: Dr. Morgan, what can you tell us about the lung parenchyma? Were there any small lymphomatous deposits there?

DR. MORGAN: No; there were not.

DR. KELLER: Was there a hydrothorax in the right side of the chest? Was there any explanation for the dullness there at the end?

DR. MORGAN: There was no hydrothorax, and the lungs showed only moderate congestion and edema.

CASE 41362

PRESENTATION OF CASE

A seventy-three-year-old widow was admitted to the hospital because of loss of appetite of two weeks' duration.

Three months before admission she began to experience an oppressive feeling in the chest as though there was something substernally that she wanted to

cough up. She coughed rarely, however, and did not bring up sputum. Fifteen days before admission she had the sudden onset of chills, a maximum temperature of 102°F., malaise and anorexia. She had been depressed for several months, and with the onset of these symptoms, depression became severe. She also complained of pain in the right flank and had several bouts of vomiting. Her physician found pus in the urine. Treatment with Gantrisin brought the temperature down, but the patient did not regain her

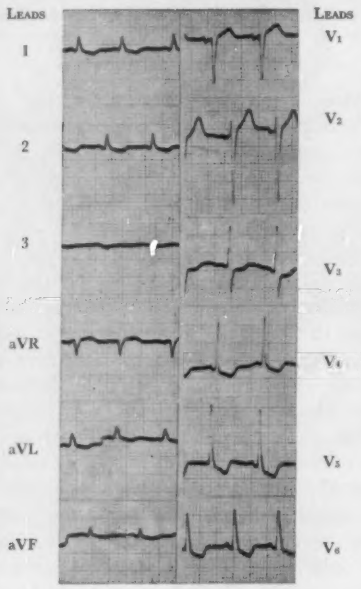

Figure 1.

appetite or recover from her depression. Diabetes, which had been discovered fifteen years before admission, had been controlled by diet for seven years and for the remaining period by gradually increasing doses of insulin. Urine tests had been blue until the onset of symptoms two weeks before admission, when they became green; during the three days before admission tests were brick red despite an increase of the NPH insulin to 35 units daily. On the morning of admission she was cold and sweaty, complaining of nonradiating oppression in the chest and shortness of breath. The temperature was 102°F.

The patient had had "gall-bladder attacks" with pain in the right upper quadrant for about thirty years. Fifteen years before admission she had a left-sided hemiparesis that cleared, leaving only slight lid drop and slight weakness of the left leg. Three years and two years before entry she had transmetatarsal amputations for gangrene. She denied ever having had an insulin reaction or ever having been in acidosis or coma. She had drunk excessive quantities of alcohol for years.

Physical examination showed a well developed and well nourished woman who did not appear uncomfortable. The neck veins were distended for 3 cm. and pulsating. There were fine, moist rales over the lower portions of the lungs and dullness over both bases. The heart was not enlarged, and the rhythm was regular. The aortic second sound was equal to the pulmonic. There was a Grade 2 apical systolic murmur. The liver was 4 cm. below the right costal margin, but not tender. There were no masses and no tenderness in the abdomen. There was ++ edema of the legs extending to the knees.

The temperature was 99°F., the pulse 85, and the respirations 20. The blood pressure was 104 systolic, 76 diastolic.

The urine had a specific gravity of 1.016 and gave a + test for albumin and a brown sugar reaction. There was no diacetic acid, acetone or bile; the sediment contained many white cells in clumps. The hemoglobin was 8.0 gm. per 100 cc., and the white-cell count 40,500, with 92 per cent neutrophils. The hematocrit was 31 per cent. The blood sugar was 430 mg., the nonprotein nitrogen 45 mg., the total protein 4.5 gm., the albumin 2.5 gm., the globulin

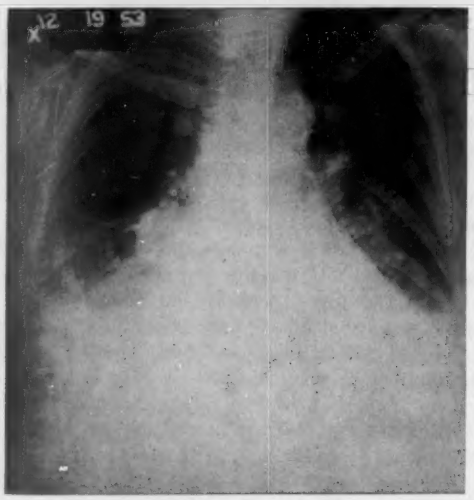

Figure 2. *Posteroanterior Roentgenogram of the Chest, with Evidence of Marked Cardiac Decompensation.*

2.0 gm., and the cholesterol 157 mg. per 100 cc.; the carbon dioxide was 24 milliequiv., the sodium 129 milliequiv., the chloride 97 milliequiv., and the potassium 5.4 milliequiv. per liter. Cephalin flocculation was negative in twenty-four and forty-eight hours. An electrocardiogram taken on the day of admission showed a normal sinus rhythm at a rate of 100; the PR and QRS intervals were normal, the ST segment sloping in Leads 1, 2, aVL, aVF, V_2, V_4, V_5 and V_6, and the T waves biphasic in Leads 1, 2, aVL, aVF, V_4, V_5 and V_6 (Fig. 1). In a second tracing taken later the same day the ST-segment changes were more pronounced. A roentgenogram of the chest revealed some enlargement of the heart. The pulmonary vessels were considerably enlarged, and there was a considerable amount of fluid in each pleural space, more on the right (Fig. 2). In a plain

film of the abdomen the kidney outlines appeared to be normal. There were two calcified bodies in the right upper quadrant of the abdomen, probably gallstones (Fig. 3). The tip of the liver lay just above the iliac crest.

The patient was given 1000 cc. of whole blood, which brought the hemoglobin up to 12 gm., a level that was maintained. During the transfusion she suddenly became cold, sweaty, tachypneic and nauseated. The temperature fell to 95°F. by rectum though the blood pressure was maintained. She began to recover after a few minutes. The next day the serum was clear, and the urine did not contain hemoglobin or casts. Insulin was given according to tests, and the diabetes controlled without difficulty. Penicillin and streptomycin were started, and Chloromycetin (chloramphenicol) added later, but the urine remained full of pus cells, and the temperature continued to range between 98 and 100°F. A urine culture grew out *Escherichia coli*. Digitalis, Mercuhydrin and ammonium chloride were given, but although some diuresis was achieved, the congestive heart failure proved intractible. The neck veins became more markedly distended, and the liver remained large and tender. Urine output was good. On the fourth hospital day a pericardial friction rub was heard, but this was not heard subsequently. The blood pressure ranged from 115 systolic, 75 diastolic, to 130 systolic, 70 diastolic, with a 6-10-mm. pulsus paradoxicus. The thorax was twice tapped, 500 and 1000 cc. of straw-colored fluid with a specific gravity of 1.010 and a total protein of 1.5 gm. per 100 cc. being removed. No tumor cells were found in a cell block. An electrocardiogram taken on the fourth hospital day showed that the T waves had become upright in Leads 3 and aVF, low in Lead V_2 and inverted in Lead V_3.

On the sixth hospital day there was fibrillation, which later reverted to normal with quinidine. An electrocardiogram at this time confirmed the physical finding of atrial fibrillation and also showed digitalis effect and nonspecific ST-segment and T-wave changes without definite evidence of infarction.

On multiple occasions throughout the hospital stay the patient complained of right-upper-quadrant pain; however, repeated abdominal examinations failed to elicit more than mild tenderness over the liver area. No masses were palpated, and peristalsis remained active. There was a persistent leukocytosis, the lowest count recorded being 15,000, and on the seventh hospital day the white-cell count was 25,000. The temperature curve was irregular, ranging from normal to 101°F. The specific gravity on four additional urinalyses ranged from 1.005 to 1.016; only one of these gave a + test for albumin, but all showed 20 to 30 white cells with clumps per high-power field in the sediment. Early on the ninth hospital day she again complained of right-upper-quadrant pain, and several hours later the blood pressure had fallen from between 120 and 130 systolic to between 100 and 110 systolic. Pulse and respirations were faster; the patient was cold, clammy and orthopneic. The neck veins pulsated, and the legs were cold and mottled. She was given Demerol and Mercuhydrin; however, her condition worsened during the next few hours. The pulse and blood pressure became unobtainable; the chest was clear, with fluid up to about the tenth intercostal space bilaterally. The heart sounds were distant without rub or gallop. On being questioned she complained of pain in the anterior part of the chest but not of abdominal pain. A short while later she died.

FIGURE 3. *Roentgenogram of the Abdomen, Showing Two Widely Spaced Annular Calcifications in the Right Upper Quadrant That Have the Appearance of Gallstones (Arrows).*

DIFFERENTIAL DIAGNOSIS

DR. GORDON D. WINCHELL*: This elderly, diabetic woman presented a clinical picture with two prominent features. She was admitted to the hospital in what appeared to be classic congestive heart failure with pulmonary congestion, bilateral pleural effusions, peripheral edema, distended neck veins and hepatomegaly. The second feature was that of fever and leukocytosis of considerable degree, indicating a systemic reaction to severe infection or breakdown products from some other tissue process.

Three months previously she had begun to experience "an oppressive feeling in the chest as though there were something substernally that she wanted to cough up." There was no mention of duration, radi-

*Clinical assistant in medicine, Massachusetts General Hospital.

ation of the pain or its relation to breathing and exertion, which would help me evaluate the underlying cause. One certainly must consider the possibility of coronary insufficiency in a seventy-three-year-old diabetic patient who had already manifested arteriosclerotic disease in the feet and central nervous system, but the description quoted above is an unusual one for coronary pain. Coronary disease could have produced the congestive heart failure without the appearance of a typical coronary pattern on the electrocardiogram but I would not expect this alone to cause the persistent fever and high white-cell count.

Two weeks before admission the sudden onset of chills, a temperature of 102°F., right-flank pain, anorexia and vomiting developed. This is suggestive of acute cholecystitis, which might be supported by the history of gall-bladder attacks for many years and the presence of opaque shadows consistent with gallstones in the x-ray films of the abdomen. The absence of localizing signs in the gall-bladder area and evidence of hepatic dysfunction tends to rule this out. We have no clear-cut evidence of either a secondary liver abscess or a subhepatic or a subdiaphragmatic abscess. The clinical picture described above, coupled with pyuria and a positive urine culture for *Esch. coli*, is entirely consistent with pyelonephritis. I think I can state that the patient had a urinary-tract infection, but the extent to which this accounted for the septic course and the congestive heart failure is less certain. The nonprotein nitrogen was remarkably low for an elderly diabetic patient in congestive heart failure, and at the time of admission there was apparently no significant uremic factor in the clinical picture. The x-ray films of the abdomen revealed normal kidney shadows, without evidence of retroperitoneal infection or tumor. I wonder if Dr. Hanelin would comment on the x-ray films.

DR. JOSEPH HANELIN: Films of the chest on admission give evidence of cardiac enlargement and congestive heart failure (Fig. 2). There are bilateral pleural effusions, greater in amount on the right.

The abdominal film indicates the presence of a greatly enlarged liver, the right margin reaching almost to the iliac crest. There is extensive calcification of the branches of the celiac axis and of the proximal portion of the superior mesenteric artery. The pelvic and femoral vessels also show calcification of their walls. Two annular calcifications, each 1.5 cm., having the appearance of gallstones, are present in the right upper quadrant (Fig. 3). These are separated by almost 5 cm.

DR. WINCHELL: Is the wide spacing between the gallstones of significance?

DR. HANELIN: Yes; this suggests that the gall bladder is of considerable size and may be pathologically enlarged.

DR. WINCHELL: The calcified bodies in the right upper quadrant are consistent with gallstones but not renal stones. Echinococcus cysts of the liver are possible but seem unlikely. The liver was enlarged on x-ray and physical examination; its description varied from that of "tender" to "nontender" during the course of the illness, but at no time was there marked tenderness or spasm. I am satisfied that this finding can be adequately explained on the basis of passive congestion and fatty changes in the liver.

The presence of a hemoglobin of 8 gm. per 100 cc. on admission brings up the question of blood loss, but this is probably best explained by infection and possibly some hemodilution in that the level was brought up to 12 gm. with only 1000 cc. of whole blood. There was no report of a blood culture in the protocol, but except for an apical systolic murmur together with the anemia, there were no findings to indicate bacterial endocarditis, which is the best single diagnosis capable of explaining all features of this case, including the anemia and febrile course with marked leukocytosis associated with congestive heart failure. Although there was evidence of urinary infection there was no comment regarding the presence of hematuria or peripheral systemic embolic phenomena. From the description of the cardiac findings one cannot assume the presence of rheumatic or congenital heart disease, in the absence of which bacterial endocarditis is less likely. However, the failure could be explained on the basis of secondary myocardial damage or progressive involvement of the heart valves. From the description at hand we have no evidence of such an involvement.

As I mentioned in the first part of the discussion coronary disease could not explain the entire picture. A review of the electrocardiograms reveals varying, nonspecific T-wave changes and varying degrees of ST-segment depression, but no clear-cut pattern of myocardial infarction (Fig. 1). Although a pericardial friction rub was heard for a short period on the fourth day there was nothing to suggest diffuse pericarditis or myocarditis. This could represent an area of subpericardial damage or an adjacent pulmonary infarct. During the relatively short hospital course the patient experienced several acute episodes, the last of which was associated with pain in the anterior part of the chest and a shocklike picture. A dissecting aortic aneurysm might be considered, but the course was somewhat prolonged and that condition does not satisfactorily explain the apparently septic course.

In any case of sudden onset of congestive heart failure associated with fever and leukocytosis one must consider the presence of pneumonia or pulmonary emboli and pulmonary infarction. Infarction is the more common and fits the protracted course, the refractory failure and the apparent acute episodes. There is no mention of any evidence of phlebothrombosis, which frequently occurs before the final episode. However, this is not necessarily so, and the other evidences of pulmonary embolization, such as cough, hemoptysis, pleurisy and cor pulmonale, are also frequently missing.

I therefore favor the following diagnoses: diabetes mellitus, generalized arteriosclerosis, coronary arteriosclerosis, with possibly patchy areas of myocardial damage, multiple pulmonary emboli and cholelithiasis. I believe that chronic pyelonephritis was present but was not a significant feature in the terminal illness.

Clinical Diagnoses

Myocardial infarction, with extension.
Arteriosclerotic heart disease and congestive heart failure.
Anemia, unknown etiology.
Diabetes mellitus.
Pyelonephritis.
Cholelithiasis.

Dr. Gordon D. Winchell's Diagnoses

Coronary arteriosclerosis, with ?myocardial damage.
Pulmonary emboli.
Diabetes mellitus.
Generalized arteriosclerosis.
Cholelithiasis.
Chronic pyelonephritis.

Anatomical Diagnoses

Coronary-artery disease, with old and recent coronary occlusions and old and recent myocardial infarcts.
Cholecystitis, acute and chronic, with rupture and abscess formation.
Cholelithiasis.
(Diabetes mellitus.)
Pyelonephritis, chronic.
Diabetic glomerulosclerosis.
Pericarditis, fibrinous.

Pathological Discussion

Dr. Edgar B. Taft: It is a little bit difficult for me to decide what was the primary anatomical cause of the death of this patient. She had both heart disease and gall-bladder disease. There was a recent acute myocardial infarction, which involved the anterior half of the septum and a small area of the anterior wall of the left ventricle. Grossly, this was yellow and mottled with red and was adjacent to a small area of old fibrosis also in the anterior wall of the left ventricle. Microscopically, the myocardium showed changes quite consistent with a lapse of three or four weeks, and I wonder if the episode of fever and malaise fifteen days before admission had its basis in this area of infarction. In addition there was an acute fibrinous pericarditis associated with this infarction. The coronary arteries leading to this area were markedly sclerotic and narrowed, but there were no thrombi. In the circumflex branch of the left coronary artery, 2 cm. from its origin, there was an occlusive thrombus, which was firm, red gray and well attached. It is a bit unusual to find thrombi not directly associated with an infarct, but, as pointed out by Blumgart, Schlesinger and Davis,* there are frequently thrombi in the coronary vascular tree that produce infarction although the thrombus actually may not be in the vessel leading to the area that has become infarcted. This is because of the generalized embarrassment of the coronary circulation by arteriosclerosis so that when there is an additional decrease in collateral circulation, infarction occurs. In this case the circumflex branch had apparently been the collateral vessel that was supplying the myocardium usually supplied by the descending branch.

The gall bladder was the site of acute inflammation. It was ruptured, with loss of the majority of its anterior wall. There were two gallstones, one in the bladder near the cystic duct and one out in the center of an abscess cavity beside the gall bladder. In addition to the abscess involving the gall bladder there were several adjacent abscesses, which were loculated and interconnected. All had dense fibrous walls and had apparently been present for some time; I do not know exactly how long, but certainly weeks. These together held about 100 cc. of creamy, purulent exudate. In turn these cavities were connected with a fresh abscess, which was lined by fibrinous exudate and lay between the stomach and the left lobe of the liver. This was partially walled off by the omentum, as were all the other abscesses. The liver showed a moderately severe pericholangitis and occasional microscopic abscesses, but there was no evidence of obstructive jaundice.

In addition to these findings the kidneys showed moderate but quite inactive pyelonephritis, with fairly marked nephrosclerosis. There was prominent glomerulosclerosis of the sort associated with the Kimmelstiel–Wilson syndrome although clinically the patient did have the edema and albuminuria associated with this syndrome. She showed only a very small amount of albumin in the urine on one or two occasions.

There was fluid in the thorax, and the lungs showed minimal to moderate congestion and edema; they were not at all heavy. There was no evidence of pulmonary emboli or of infarction or pneumonia.

A Physician: Dr. Currens, would you have suspected a myocardial infarction?

Dr. James H. Currens: I think the changes in the electrocardiogram were minimal and could go with pericarditis or myocardial infarction. In my opinion the duration of pain over a period of three months would be quite unusual with pericarditis. I have the impression that the pain was intermittent.

Dr. Taft: The more recent infarction certainly was not three months old although there was an area of fibrosis that I suspect could have been anywhere from several months to several years old.

*Blumgart, H. L., Schlesinger, M. J., and Davis, D. Studies on relation of clinical manifestations of angina pectoris, coronary thrombosis and myocardial infarction to pathologic findings, with particular reference to significance of collateral circulation. *Am. Heart J.* 19:1-91, 1940.

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HELL-BENT FOR ELECTION

PUBLISHED elsewhere in this issue of the *Journal* is a brief, clear and comprehensive description of the expansion of compulsory social security from the beginning in Europe of its modern phase, late in the nineteenth century, to the system in operation in this country at the time of the recessing of the first session of the Eighty-Fourth Congress in August, 1955. Prepared as part of a longer report by the Committee on National Legislation of the Massachusetts Medical Society, now under the able chairmanship of Dr. Carl F. Maraldi, it is presented here as a matter of general information on a subject that is both important and confusing as each new Congress extends the benefits and increases the liabilities of the program.

The Committee has well analyzed the more important of the medical-social-economic problems with which congressmen have to tussle and that have a definite bearing on the practice of medicine and its practitioners. Its reports are designed to inform and enlighten the busy physician, who, obviously, cannot keep pace with the complex Washington scene and the activities of the social planners who with misguided beneficence are attempting to lead the Government into the practice of medicine.

The busy practitioner, however, unless he becomes personally involved, must leave the more detailed study and action to be taken on these innumerable medical measures to those confreres willing to serve on the Committee on National Legislation and to his more remote representatives in the Washington office of the American Medical Association. He continues his daily practice only slightly aware of the legislative struggle about him. Occasionally, he may be more consciously aware of the gathering storm when he hears a distant thunderclap in the form of a newspaper, radio or TV account of a "blast" against something or other by the American Medical Association. He then turns back to his practice, blithely secure in the happy thought that his elected medical representatives will nicely handle his elected political representatives.

Unfortunately, as evidenced by the Eighty-Fourth Congress in its first session, his medical representatives cannot by themselves stem the increasing political encroachment on the practice of medicine. Whether or not organized medicine as represented by the American Medical Association is losing some of its rightful influence in Washington is still a matter of conjecture. The discriminatory doctor's draft was extended despite formidable opposition by the Association. Compulsory social-security coverage for physicians came within a whisker of being passed and will certainly be a hot issue when the Congress reconvenes. The Administration has given high priority to passage of legislation for reinsurance of voluntary health plans during the forthcoming second session.

It may be that the elected congressional represen-

tatives, so familiar now with the sound (and sometimes fury) of the ever-present voice of organized medicine, are no longer awed — if, indeed, they ever were — with its power and might. It may be that the members of Congress believe that the familiar voice of the American Medical Association is not echoing the opinions of the busy medical practitioner, and there is always present the necessity of pleasing a majority of the voters.

Perhaps too much impersonality is causing some of organized medicine's difficulty in Washington. If such is the case, political intervention in the practice of medicine will not be deterred unless Congress can be assured that the voice of organized medicine is the personal voice of the practicing physician.

The *Journal* will attempt from time to time in these columns to keep its readers posted on pertinent legislation pending before Congress, presenting both sides of the problem as fairly as is humanly possible with the hope that the busy practitioner will take the time to study the problem and to act upon it by contacting his Congressional representatives on a personal basis.

NOT TO HARM

THE *Journal*, on June 23, published an article reporting a case of anuria following the routine administration of phenylbutazone. The fact that the patient died of myocardial infarction and pulmonary embolization after recovering from the renal complication does not directly implicate phenylbutazone as the lethal agent in this case, but does add another to the unhappy list of those succumbing during or subsequent to its use.

Elsewhere in this issue Mauer presents a more formidable collection of 24 deaths following the use of phenylbutazone, including 1 of his own. Among the apparent side effects of the drug, unpredictable in their occurrence and too often fatal in their outcome, are acute peptic ulcer with hemorrhage and possibly perforation, bleeding from the gastrointestinal tract of undetermined origin, toxic hepatitis and agranulocytosis.

Opposed to these risks are the claims that 57.6 per cent of patients suffering from rheumatoid arthritis have "remissions" or "major improvements" in response to the administration of the agent. Neither phenylbutazone nor any other drug as yet discovered "cures" arthritis in any of its forms, although phenylbutazone is said to be of considerable value in the treatment of gout.

With deliberate oversimplification, powerful drugs may be classified according to their therapeutic value and their ill effects. There are those of tried and proved merit and of reasonably predictable toxicity. Among them may be listed the arsenical compounds, mercury, quinine, opium and digitalis and some of the more recently discovered agents of high repute and inestimable value.

There are, in addition, — products of the new pharmaceutic era in medicine, — a host of elaborate and variously effective compounds, some of which have proved to be of unexpected and unassessable toxicity. The medical profession must be constantly on the alert to retain clinical control of this pharmaceutic output, bearing in mind the aphorism that the physician must at least subject his patients to no risks that are not justified by the good that may be accomplished. In short, any drug that is to be used over considerable periods of time and that has toxic propensities should be carefully evaluated by the physician before he embarks upon a course of chronic treatment with it. As a corollary, drugs that have highly toxic possibilities that may result in fatalities should be reserved mainly for situations where they exert a dramatic or almost curative effect.

Finally, the terms in which they are advertised to the medical profession should be conservatively realistic and contain clear indications of the risks involved.

MASSACHUSETTS ACADEMY OF GENERAL PRACTICE SYMPOSIUM ON MASS CASUALTIES

SHOULD an enemy attack this country, the average practitioner of medicine will find himself completely and irrevocably involved in a problem about which he has heard much, read some, and knows but little — the management of mass casualties on a scale limited only by the destructive power of the latest thermonuclear blast.

To forearm the forewarned practicing physician on matters of mass casualties, the Massachusetts Academy of General Practice, at the afternoon session of its fall clinical assembly, Saturday, September 24, at the Hotel Statler in Boston, will sponsor a symposium on the management of mass casualties, to be presented by the Office of the Surgeon General, Department of the Army.

The chairman of the symposium, which all physicians, hospital administrators and civilian defense officials are invited to attend, will be Brigadier General James P. Cooney, MC, deputy surgeon general, United States Army.

In addition to dramatic exhibits and demonstrations, the symposium will feature talks by specialists in Army medicine on weapons effects and the anticipated medical program; first aid and emergency medical care; hospital organization; management of trauma; and psychologic considerations in nuclear warfare.

The Massachusetts Academy of General Practice is to be commended on having arranged for such a presentation in Boston. Attendance at this symposium should be a *must* for every physician aware of the implications of an enemy attack on this country but only vaguely aware of the role he will have to assume in the management of mass casualties.

Physicians engaging in the service of Russia, cannot always relinquish their engagements at pleasure . . . there are quite a number of young American physicians engaged in the Crimea, and some of them in Sebastopol, who cannot hope for release before the end of the war, lest they should impart information to the disadvantage of the Russians . . . In the allied armies there are no such restrictions upon the personal liberty of physicians.

Boston M. & S. J., *Sept. 13, 1855*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Aspiration of Gastric Contents

A twenty-three-year-old gravida II, para I, was admitted to the hospital at term in early labor. The time of her last meal was unknown but she vomited some undigested food before medication, which was started shortly, Seconal, Demerol and scopolamine being given in moderately large amounts. Nitrous oxide, oxygen and ether anesthesia, with closed carbon dioxide absorption technic, was started by a physician anesthetist fifteen hours after admission.

Vomiting occurred during induction; the material was removed by suction, and anesthesia was then resumed for normal delivery of an infant weighing 4.2 kg. (9 pounds, 4 ounces). The third stage was normal. No hemorrhage occurred, and a pulse recorded one hour post partum was 104, and the respirations were 20.

However, two and a half hours post partum, additional vomiting occurred, and marked cyanosis was noted. The pulse rate was extremely rapid, and the respirations were 52. A good deal of brown, blood-tinged fluid was aspirated by endotracheal tube, but a bronchoscopist was not called until almost two *more* hours passed. When he arrived, the patient had just died.

This case was classified as a preventable death and subclassified as an anesthetic death. It seems clear that the patient died from the aspiration of gastric contents, the primary avoidable factor. But, even so, prompt bronchoscopy (performed within half an hour) never fails to correct the situation. Therefore, the delay in calling a consultant, combined with what appears to have been inadequate post-partum observation, aggravated what need not have been more than a transient complication.

John Figgis Jewett, M.D.
Chairman

EXTENSION OF SOCIAL SECURITY

The following abstract from a report of the Committee on National Legislation has been submitted for publication by the chairman, Dr. Carl F. Maraldi.

Economic insecurity is a by-product of industrialization. Removed from the soil a working man may become subject to the vagaries of an economic system over which he as an individual has little or no control. It is not surprising, therefore, that public and private schemes designed to alleviate the hazards of unemployment and subsequent impoverishment have been in vogue in industrial areas since the late Middle Ages.

The first system of compulsory unemployment compensation was established in England in 1912. The German system, after which that of the United States is patterned, was adopted in 1927. The first system of compulsory old-age and invalidity insurance was adopted in Germany in 1889, and that of Great Britain dates from 1925. Denmark established the first noncontributory old-age-assistance law in 1891.

Compulsory social security in the United States came into being during the depths of the depression. Under the Social Security Act of 1935 three programs were established. One of these — Public Assistance — was outright charity; the other two — Old Age and Survivor's Insurance and Unemployment Compensation — were contributory, with the employer and employee sharing the monthly contributions.

Under Public Assistance federal grants-in-aid are made to the states on a matching basis for dependent children, the aged, the blind and, since 1950, the permanently and totally disabled.

Under Old Age and Survivor's Insurance, benefits are provided for covered employees who retire at sixty-five years of age or older, for wives and widows of covered employees when they have reached the age of sixty-five years and for widows and surviving children of covered employees until the youngest child becomes eighteen years old.

Physicians are especially interested in social security because a full-scale social-security program includes federal compulsory health insurance. According to the International Labor Office the contingencies to be covered by such a full-scale program as follows*:

1. Sickness
2. Maternity
3. Invalidity
4. Old age
5. Death of breadwinner
6. Unemployment
7. Employment injuries
8. Emergency expenses for
   a. Housewives with dependent children while unable to keep house during hospitalization
   b. Clothing and other equipment associated with childbirth
   c. Helpless invalids needing constant attention
   d. Cost of a simple funeral

In the United States the initial attempt to expand the Social Security Act of 1935 in accordance with the recommendations of the International Labor Office was contained in the first Wagner–Murray–Dingell Bill, which was introduced in 1943 (S. 1161-78th Congress, 1st Session). This bill would have created a unified national social insurance system composed of the following:

1. A system of employment offices
2. Expanded old-age retirement insurance benefits
3. Expanded survivor's insurance benefits
4. Permanent disability insurance benefits
5. Lump-sum death payments
6. Protection to individuals in military service
7. Expanded unemployment insurance benefits and allowances

**Social Security: Principles and problems arising out of the War.* Montreal & International Labor Office, 1944.

8. Temporary disability insurance benefits
9. Maternity insurance benefits
10. Medical and hospitalization insurance benefits

According to the International Labor Office:

> Universality of scope [persons covered] is of the essence of the modern conception of social insurance as illustrated in the Beveridge and Marsh reports and the Wagner–Murray–Dingell Bill, and as practiced in Denmark and New Zealand . . . Only by aiming at universality will it be possible to create a social insurance system under which the citizen as worker achieves the status of effective partnership in society by contributing his quota to its resources and receiving in return from the State the opportunity to work and maintenance when he cannot work. Hitherto the great majority of social insurance schemes have been limited to employed persons. They are therefore class measures, not national schemes. There are two important practical reasons for this limitation. The first is the difficulty of collecting contributions from persons who have no employer, and the second is to find a substitute for the employer's contribution. A further relevant consideration is that sickness and unemployment benefits — not to mention compensation for employment injuries — have been designed to cover the needs of employed persons only, and the technique of affording similar protection to other gainfully occupied groups remains to be developed. The first two difficulties are real but not insuperable. For the third, only partial solutions can be offered.

Initially, a number of numerically important classes were excluded from insured coverage under the Social Security Act. These included agricultural laborers; domestic servants in private homes; casual workers; self-employed persons or persons working on their own account; employees of private nonprofit religious, charitable, scientific or educational agencies; employees of state governments or their instrumentalities; employees of the Federal Government; and employees of the railroads covered under the Railroad Retirement Act. As a result of recent amendments agricultural laborers, domestic servants and certain employees of private nonprofit agencies have been included on a compulsory basis, and members of the clergy on a voluntary basis. At present the pressure for universal compulsory coverage of all who earn is becoming more and more intense.

STATED MEETING OF THE COUNCIL

A stated meeting of the Council will be held in John Ware Hall, Boston Medical Library, 8 Fenway, Boston, on Wednesday, October 5, at 10:30 a.m.

Business:

1. Call to order at 10:30 a.m.
2. Presentation of record of meeting held May 16, 1955, as published in Vol. 253, Supplement No. 1, July 7, 1955, of the *New England Journal of Medicine*.
3. Reports of standing and special committees.
4. Such other business as may legally come before this meeting.

ROBERT W. BUCK, M.D.,
Secretary

DEATH

SLAUGHTER — Emma Young Slaughter, M.D., of Lowell, died on July 18. She was in her eighty-second year.

Dr. Slaughter received her degree from Tufts University School of Medicine in 1898. She was a fellow of the American Medical Association.

She is survived by a sister and a brother.

BOOK REVIEWS

Amputations. By Leon Gillis, M.B.E., M.B., B.Ch. (Witwatersrand), M.Ch. Orth. (Liverpool), D.L.O. (London), F.R.C.S. (England), F.R.C.S. (Edinburgh), Hon. F.I.C.S. (Geneva). 8°, cloth, 423 pp., with 342 illustrations, some in color. New York: Grune and Stratton, 1954. $12.75.

From his wide experience at a large rehabilitation center the author has written a most practical and helpful book. He is careful to show in this work that an amputation requires detailed planning and preparation, technical skill and a long period of training afterward, to ensure good function and proper use of the limb. All types of amputations and their many problems and complications are discussed and illustrated.

A useful chapter discusses congenital deformities, particularly partial loss of a limb, how it can be improved surgically and the types of prostheses that are advised. There is an unusual but most rewarding chapter on the nursing care of patients with amputations. The book is profusely illustrated with clear and well chosen pictures. Each chapter is followed by an adequate bibliography.

Although surgeons will not agree with all the author's conclusions regarding amputations, their location and type it must be admitted that the book is well written and is a most thoughtful treatise. This is a useful textbook for this type of surgery. It is particularly recommended for the surgeon who performs amputations only occasionally, since it is well for him to remember that the surgery itself is only a small part of the treatment in regaining function after the loss of a limb or a part of it.

JOHN G. KUHNS, M.D.

Medical Treatment of Mental Disease: The toxic and organic basis of psychiatry. By Daniel J. McCarthy, M.D., LL.D.; and Kenneth M. Corrin, M.D. 8°, cloth, 653 pp., with 30 illustrations and frontispiece. Philadelphia: J. B. Lippincott Company, 1955. $12.00.

Everyone who deals daily with the problems of mental illness realizes that it is easy to lose sight of the forest because of the trees. But discerning physicians will remember that the study and treatment of mental disorder is rapidly and constantly changing. Beginning with the great psychiatric Renaissance initiated by Freud, Jung and Adler in the late 1890's and the first ten years of this century, the geographic outline of psychiatry has changed strikingly every ten years. A hundred years ago the "moral treatment" of mental disorder was initiated in Massachusetts by a small number of far-sighted state-hospital superintendents. There was subsequently a period when many assumed that mental disorders could be treated by mental methods alone such as suggestion, persuasion and emotional re-education. Then, the remarkable physical methods of treatment of mental illness were discovered — electroshock, insulin and now lobotomy. Today, conservative psychiatrists of wide experience realize that all these methods are valuable, and it remains for future investigation to determine just what method or combination of methods is most effective in the treatment of a particular disorder.

This new book by Dr. Daniel J. McCarthy and Dr. Kenneth M. Corrin brings together practically everything that is known on this subject. It represents an enormous accomplishment, which was achieved with the help of eight other contributors, all of them Pennsylvania specialists in the treatment of mental illness. The book starts with the keynote struck in the nineteenth century by Dr. Silas Weir Mitchell; the frontispiece is the Vonnah portrait of Dr. Mitchell. The preface, prepared jointly by the authors, is an excellent essay in itself, full of affirmation and determination to cement all possible methods, physical and psychologic, that can help in the treatment of mental disease. Stressing particularly the medical treatment of mental disease, this book is remarkably well organized into five basic parts, which include the physical bases of psychiatry, the cause of mental disorder, the occurrence of mental disorders and two sections dealing with the examination of the patient and the subject of personality. The whole book is extremely

orderly and well arranged. Under each of these five parts, in detailed subdivisions, the authors and contributors have accumulated specific methods of diagnosis and treatment, which make this book almost an encyclopedia of the diagnosis and treatment of mental illness. Particularly valuable is the fourth part, on basic treatment methods. One does not often find this material so well presented. In detailed and simple language, a great amount of information about sedatives, hydrotherapy, occupational therapy, psychiatric nursing and other factors are presented, and the following chapter on psychotherapeutic measures is extremely informative and valuable. The book is written from a broad and unbiased point of view. Everything is included, nothing is omitted, there is a place for everything, and everything is in its place. The book ends with a section on the medicolegal aspects of psychiatry.

All in all, this book now stands as one of the best on general psychiatry published to date in the United States. It would make an ideal gift for a physician who likes to keep his psychiatric library complete, or a gift for a young man entering or graduating from medical school.

MERRILL MOORE, M.D.

Fractures in Children. By Walter Putnam Blount, M.D. 4°, cloth, 279 pp., with 311 illustrations. Baltimore: Williams and Wilkins, 1954. $9.50.

Many excellent books have been written on the treatment of fractures, but none have been devoted wholly to fractures in children. There is a distinct need for a book of this sort because, with growth of the skeleton, injuries to the bones lead to special problems. Injuries to the epiphyses often cause interference with growth and may result in deformity. Most fractures in children, as the author states, heal well, often with indifferent treatment; nonunion is practically unknown. Alignment of the fragments is the chief requirement, although bowing is often corrected with growth.

As the writer shows, excellent results are obtained in most cases by traction or by closed reduction and cast. Physiotherapy is almost never necessary in children. All types of fractures found in children are covered adequately and succinctly. The figures and photographs are good. An adequate bibliography is added. This book can be recommended without reservation as an adequate guide in the treatment of fractures in children.

JOHN G. KUHNS, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Handbook of Medical Treatment. Edited by Milton J. Chatton, M.D., director of medical institutions, Santa Clara County, California, superintendent of Santa Clara County Hospital, San Jose, California, and assistant clinical professor of medicine, University of California School of Medicine; Sheldon Margen, M.A., M.D., associate research biochemist, Department of Physiological Chemistry, and clinical instructor in medicine, University of California School of Medicine, San Francisco; and Henry D. Brainer, M.D., William Watt Kerr Associate Professor of Clinical Medicine, University of California School of Medicine, San Francisco, visiting physician and chief of Medical Service, San Francisco Hospital. Fourth edition. 12°, paper, 568 pp., with illustrations. Los Altos: Lange Medical Publications, 1954. $3.00.

This new edition of a standard manual has been considerably revised and expanded. There is a good index. The handbook should prove useful to the practicing physician for quick reference.

The Management of Endocrine Disorders of Menstruation and Fertility. By Georgeanna Seegar Jones, M.D., assistant professor of gynecology, Johns Hopkins University School of Medicine, and gynecologist, Johns Hopkins Hospital, Baltimore, Maryland. 8°, paper, 198 pp., with 37 figures. Springfield, Illinois: Charles C Thomas, 1954. $5.75 (Publication No. 206, *American Lecture Series.)*

The author discusses the pituitary and ovarian hormones, chorionic gonadotrophin, the menarche and menopause, normal and pathologic manifestations of menstruation and tumors of the chorion. The literature has been surveyed, and there is a bibliography of 344 references. There are indexes of authors and subjects. The monograph should be in all medical libraries as a reference source.

Cleft Palate and Speech. By Muriel E. Morley, B.Sc., F.C.S.T., speech therapist to the Royal Victoria Infirmary, the Hospital for Sick Children and the Newcastle General Hospital, Newcastle-upon-Tyne. Third edition. 12°, cloth, 173 pp., with 64 illustrations. Edinburgh: E. and S. Livingstone, Limited, 1954. $4.25.

A center for the treatment of cleft palates has been established at the Fleming Memorial Hospital for Sick Children in Newcastle, England, and Miss Morley has had the opportunity of examining cases at this institution. The chapters on treatment have been revised in this third edition of a book first published in 1945. There is a list of references and an index. The small book was well printed in Great Britain.

Strahlendosis und Strahlenwirkung: Tafeln und Erläuterungen-Unterlagen für den Strahlenschutz. By B. Rajewsky; with the co-operation of K. Aurand, O. Hug, H. Mergler, H. Muth, H. Pauly, A. Schraub, E. Six and I. Wolk, Max-Planck Institut für Biophysik, Frankfurt a.M. 8°, paper, 112 pp., with 2 illustrations and 79 tables. Stuttgart: Georg Thieme, 1954. $2.65.

This manual tabulates the dosage and action of the various rays used in diagnosis and treatment. There are 79 tables and 72 pages of text concerning the tables. There is a bibliography of 110 pages. The book should be in all collections on radiology.

Tabak: Betrachtungen über Genuss-und Rauschpharmaka. By Kurt Pohlisch, professor of psychiatry and neurology in Bonn. 8°, paper, 207 pp. Stuttgart: Georg Thieme, 1954. (*Arbeit und Gesundheit,* Neue Folge, Heft 54; distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Dr. Pohlisch considers tobacco smoking in relation to other intoxicants and opiates and to its poisoning effect, its psychology and pharmacology and its relation to war during 1940-1950. There is a solid bibliography of 5½ pages and indexes of names and subjects. The tobacco question is so important at present that the book should be in all medical libraries.

Biology of Anopheles Gambiae: Research in West Africa. By M. H. Holstein, Dr. ès Sc., chief of research, Office de la Recherche Scientifique Outre-Mer, Paris. 8°, paper, 172 pp., with 22 illustrations and 31 tables. Geneva: World Health Organization, 1954. $2.00.

The author presents the results of studies carried out during a period of two years principally in the Upper Volta region of French West Africa.

Of Whales and Men. By R. B. Robertson. 8°, cloth, 300 pp., with illustrations. New York: Alfred A. Knopf, 1954. $4.50.

Dr. Robertson relates his experiences as senior medical officer to one of the largest whaling expeditions of the season of 1950-1951. Based on South Georgia, he traveled 48,000 miles in eight months in search of whales. The narrative is written in an interesting manner, and the publishing is excellent. The book should be in all collections on medical biography and travel.

The Clinical Physiology of the Lungs. By Cecil K. Drinker, M.D., D. Sc. 8°, cloth, 84 pp., with 27 illustrations. Springfield, Illinois: Charles C Thomas, 1954. $5.50.

Dr. Drinker, who has been interested in the physiology of the lungs since 1921, summarized the results of his researches in a series of lectures given in 1945 and in 1950. These have now been assembled and amplified in this monograph, which should be in all collections on the physiology of the respiratory system.

The Role of the Pituitary in Cancer: The clinical value of pituitary lipid treatment. By Henry K. Wachtel, M.D. 8°, paper, 31 pp. New York: William-Frederick Press, 1954. Free.

Dr. Wachtel is director of the Chemical Hormone Corporation, New York City.

Lehrbuch der Inneren Medizin. By M. Broglie and others. Third edition revised. Vol. 2. 8°, cloth, 1042 pp., with 390 illustrations partly colored. Stuttgart: Georg Thieme, 1954. DM 49.80.

This second volume of a standard German system of internal medicine deals with the digestive and urinary organs, the locomotor and nervous systems, allergy, poisoning and diagnosis and treatment in general. The first volume, also published in 1954, dealt with infectious diseases, diseases of the blood, metabolism and internal secretions, the mediastinum and the respiratory system. The text was written by 13 German physicians of standing. The publishing is excellent, and the price is not exorbitant for this type of book.

Acta radiologica. Supplementum. Stockholm, 1954. Acta radiologica.

110. *Roentgen Examination of the Proximal Femur End in Children and Adolescents.* By Lars Billing. 4°, paper, 80 pp., with 53 illustrations. Sw. Kr. 25

111. *Cholesteatoma of the Middle Ear.* By Lars Winderen and Johannes Zimmer. 4°, paper, 119 pp., with 45 illustrations. Sw. Kr. 20.

112. *Malignant Transformation of Squamous Epithelium.* By Gunnar Moberger. 4°, paper, 108 pp., with 45 illustrations. Sw. Kr. 25.

113. *The Causal Relationship between Benign Epithelial Tumors and Adenocarcinoma of the Colon and Rectum.* By K. A. Hultborn. 4°, paper, 71 pp., with 78 illustrations. Sw. Kr. 15.

114. *The Conventional Roentgenogram in the Commonest Congenital Malformations of the Heart and Great Vessels in Adults and Juveniles.* By Georg–Fredrik Saltzman. 4°, paper, 59 pp., with 29 illustrations. Sw. Kr. 25.

115. *Cancer Cells in Urinary Sediment.* By Carl Deden. 4°, paper, 75 pp., with 19 plates. Sw. Kr. 20.

Biology of Anopheles Gambiae: Research in French West Africa. By M. H. Holstein, Dr. ès Sc., chief of research, Office de la Recherche Scientifique Outre-Mer, Paris. 8°, paper, 172 pp., with 22 figures and 31 tables. Geneva: World Health Organization, 1954. $2.00.

Expert Committee on Malaria. Fifth report. 8°, paper, 42 pp. Geneva: World Health Organization. 25¢. (*World Health Organization Technical Report Series* No. 80.)

Existence and Therapy. An Introduction to Phenomenological Psychology and Existential Analysis. By Ulrich Sonnemann, Ph.D. 8°, cloth, 372 pp. New York, New York: Grune and Stratton, 1954. $7.75.

The Permanent Revolution in Science. By Richard L. Schanck, chairman, Department of Sociology, Bethany College, and lecturer, Carnegie Institute of Technology. 8°, cloth, 112 pp. New York: Philosophical Library, 1954. $3.00.

A Synthesis of Human Behavior: An integration of thought processes and ego growth. By Joseph C. Solomon, assistant clinical professor of psychiatry, University of California School of Medicine, and consultant, Mount Zion Hospital, San Francisco, California. 8°, cloth, 265 pp., with illustrations. New York: Grune and Stratton, 1954. $5.50.

NOTICES

ANNOUNCEMENT

Dr. Julius Kritzman announces the opening of his office for the practice of internal medicine at 1152 Beacon Street, Brookline, Massachusetts.

MASSACHUSETTS ACADEMY OF GENERAL PRACTICE

The Clinical Assembly of the Massachusetts Academy of General Practice will be held at the Hotel Statler, Boston, on Saturday, September 24. Both morning and afternoon sessions will be held in the Grand Ballroom.

Program

9:00 a.m.	Office Ophthalmology. Benjamin Bell, M.D., chief, EENT Unit, Veterans Administration Out-Patient Clinic, Boston.
9:20 a.m.	Influence of Thyroid and Testosterone on Bone Growth. Joseph M. Looney, M.D., research professor of biochemistry, Boston University School of Medicine.
9:40 a.m.	Treatment of Advanced Malignant Disease. Henry M. Lemon, M.D., associate professor of medicine, Boston University School of Medicine.
10:00 a.m.	Recess.
10:20 a.m.	Hepatitis in General Practice. Thomas A. Warthin, M.D., associate clinical professor of medicine, Harvard Medical School.
10:40 a.m.	Present Status of Polio Vaccination. Samuel B. Kirkwood, M.D., Massachusetts Commissioner of Public Health.
11:00 a.m.	Office Cardiology. David Littman, M.D., chief, Cardiology Section, Veterans Administration Hospital, West Roxbury, Massachusetts.
11:20 a.m.	Surgical Office Procedures. Richard Warren, M.D., associate clinical professor of surgery, Harvard Medical School.
11:40 a.m.	The Physician in Relation to the Community Hospital. John F. Conlin, M.D., director, Boston City Hospital.
12:00 m.	What the New England Chapter, Arthritis and Rheumatism Foundation, Has to Offer the General Practitioner. Hans Waine, M.D., medical director, New England Chapter, Arthritis and Rheumatism Foundation.
12:15 p.m.	Luncheon. Parlors B and C, Mezzanine.
1:20 p.m.	Recess.
1:20 p.m.	Annual Meeting. Parlors B and C. Mezzanine.
2:00-6:00 p.m.	Symposium on Management of Mass Casualties. Presented by the Office of the Surgeon General, Department of the Army (chairman, Brigadier General James P. Cooney, MC, deputy surgeon general, United States Army).

Weapons Effects and the Anticipated Medical Program. Lieutenant Colonel James B. Hartgering, MC, chief, Department of Biophysics, AMSGS, WRAMC.

First Aid and Emergency Medical Care. Lieutenant Colonel Joseph D. Goldstein, MC, chief, Department of Atomic Casualties Studies, AMSGS, WRAMC.

Management of Trauma. Colonel Joseph R. Shaeffer, MC, surgical consultant to the Surgeon General, office of the Surgeon General, Department of the Army, Washington, D.C.

Psychological Considerations in Nuclear Warfare. Colonel Albert J. Glass, MC, deputy director, Neuropsychiatry Division, AMSGS, WRAMC.

6:15 p.m. Cocktail hour. Ballroom.

7:15 Dinner. Among the speakers will be Dr. John R. Fowler, president of the American Academy of General Practice; Brigadier General James P. Cooney, MC, deputy surgeon general, United States Army; and Dr. Alexander Marble, brigadier general, Medical Corps, USAR, clinical associate in medicine, Harvard Medical School.

MASSACHUSETTS POLIOMYELITIS EMERGENCY CARE

Massachusetts hospitals or physicians may obtain information regarding qualified physical therapists for polio patients with poliomyelitis at home or in hospitals from Nina G. Nichols, 296 Allston Street, Brookline 46, Massachusetts (telephone, ASpinwall 7-5750 or ALgonquin 4-6685). In Western Massachusetts information may be obtained from Nicholas Serino, Veterans Administration Hospital, Northampton, Massachusetts (telephone, Northampton 4040).

CANCER RESEARCH INSTITUTE

Effective August 1, 1955, the address of the Tumor Diagnosis Service was changed to the Lemuel Shattuck Hospital, 170 Morton Street, Jamaica Plain, 30, Massachusetts. The Service will continue there as in the past.

CONNECTICUT ACADEMY OF GENERAL PRACTICE

The 1955 convention of the Connecticut Academy of General Practice will be held at the Statler Hotel, Hartford, Connecticut, on Thursday, October 20. Among the speakers will be Drs. Robert L. Parker, associate professor of internal medicine, University of Minnesota Medical School; Ovid Meyer, Madison, Wisconsin; Joe W. Howland, University of Rochester; A. F. Castro, Washington, D. C.; and Harry M. Robinson, Jr., Baltimore, Maryland.

CLINICAL FELLOWSHIPS IN RADIATION THERAPY

The American Cancer Society announces the clinical fellowships in radiation therapy, available to qualified graduates in medicine who have already received thorough basic training in the principles and practice of radiation therapy and who desire to spend additional periods of training in that specialty at certain clinics in the United Kingdom, Scandinavian countries and France. A stipend of $4,500 will be awarded for a year, travel included. Application forms and further information may be obtained from the American Cancer Society, Inc., Professional Education Section, 521 West 57th Street, New York 19, New York.

AMERICAN CANCER SOCIETY CLINICAL FELLOWSHIPS

The American Cancer Society announces the continuation of the clinical-fellowship grants, available primarily to teaching institutions approved by the Council on Medical Education and Hospitals of the American Medical Association. A stipend of $3,600 will be awarded for a year. Individual applicants should apply directly to the institutions where such fellowships are available. A list of such institutions may be obtained from the National Office of the American Cancer Society. Applications must be submitted through the institution in which the work will be done to Dr. Brewster S. Miller, director, American Cancer Society, Inc., Professional Education Section, 521 West 57th Street, New York 19, New York.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER. Beth Israel Hospital Course. Page 509, issue of March 24.

SEPTEMBER 8–28. Consultation Clinics for Crippled Children in Massachusetts. Page 394, issue of August 25.

SEPTEMBER 12–15. International College of Surgeons. Page 394, issue of September 1.

SEPTEMBER 12–21, DECEMBER 5–14, 1955, JANUARY 30–FEBRUARY 8, MARCH 19–28 and JUNE 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

SEPTEMBER 14–17. Heart-Disease Seminar. Page 260, issue of August 11.

SEPTEMBER 20. Boston Tuberculosis Association. Page 394, issue of September 1.

SEPTEMBER 21. Essex North District Medical Society. Page 208, issue of August 4.

SEPTEMBER 21. New Jersey Neuro-Psychiatric Institute. Page 208, issue of August 4.

SEPTEMBER 24. Clinical Assembly of Massachusetts Academy of General Practice. Page 439.

SEPTEMBER 26–30. Venereal-Disease Course. Page 348, issue of August 25.

SEPTEMBER 29–OCTOBER 1. Institute of Psychiatric Treatment. Page 302, issue of August 18.

SEPTEMBER 30–OCTOBER 1. American Medical Writers' Association. Page 118, issue of July 21.

OCTOBER 1 and 2 and 3–6. American Academy of Pediatrics. Page 118, issue of July 21.

OCTOBER 5. Arthritis and Rheumatism Foundation. Page 208, issue of August 4.

OCTOBER 6–8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.

OCTOBER 10–21. New York Academy of Medicine. Graduate Fortnight. Page 84, issue of July 14.

OCTOBER 19 and DECEMBER 14, 1955 and FEBRUARY 15, MARCH 28 and APRIL 18, 1956. Greater Boston Medical Society. Page 208, issue of August 4.

OCTOBER 20. Connecticut Academy of General Practice. Notice above.

OCTOBER 22–26. American Heart Association. Scientific Session. Page 603, issue of April 7.

OCTOBER 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.

OCTOBER 26 and NOVEMBER 30, 1955 and JANUARY 25, MARCH 21 and APRIL 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.

OCTOBER 27 and 28. New York Medical Conference. Page 394, issue of September 1.

OCTOBER 27–29. Congress of Neurological Surgeons. Page 208, issue of August 4.

NOVEMBER 1–3. Henry Ford Hospital Symposium on Enzymes. Page 920, issue of May 26.

NOVEMBER 6–13. Second International Congress of Allergology. Page 157, issue of January 27.

NOVEMBER 7–9. Association of Military Surgeons of the United States. Page 118, issue of July 21.

NOVEMBER 11 and 12. Inter-Society Cytology Council. Page 1056, issue of June 16.

NOVEMBER 14 and 25. Course in Laboratory Diagnosis of Tuberculosis. Page 1102, issue of June 23.

NOVEMBER 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.

NOVEMBER 28–DECEMBER 2. Interim Session of the American Medical Association, Boston.

MARCH 24 and 25, 1956. American Psychosomatic Society. Page 260, issue of August 11.

MAY 3–5, 1956. American Goiter Association. Page 348, issue of August 25.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 15

THURSDAY, SEPTEMBER 15

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:45–9:45 a.m. Cardiac Grand Rounds. Yamins A, Beth Israel Hospital.

*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Thoracic Conference. Thoracic Emergencies — Medical and Surgical. Drs. Dwight E. Harken and Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.

*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.

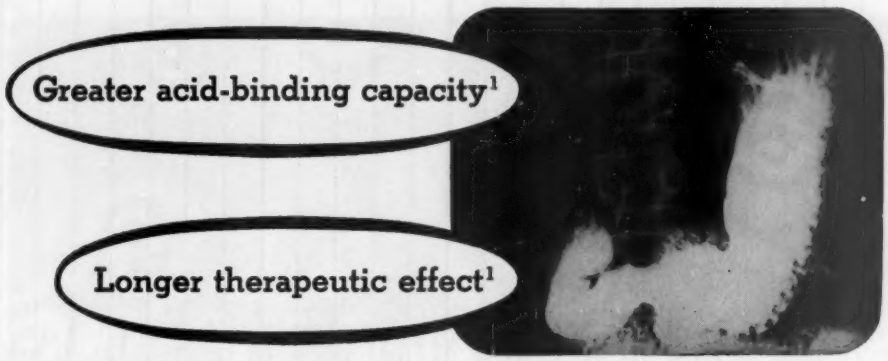
FRIDAY, SEPTEMBER 16

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

(Concluded on page xxxii)



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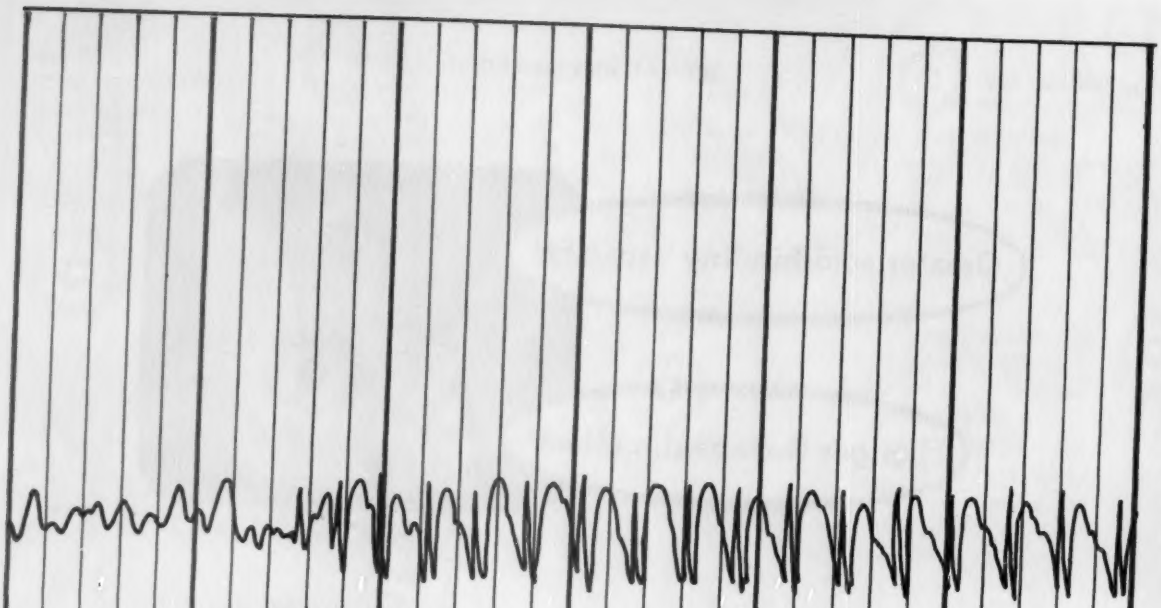
1. Rossett, N.E., Rice, M.L. Jr.: An In Vitro Evaluation of the More Frequently Used Antacids, Gastroenterology 26:490 (1954).
2. Morrison, Samuel: Magnesium Aluminum Hydroxide Gel in the Antacid Therapy of Peptic Ulcer, Am. J. Gastroenterology 22:309 (1954).



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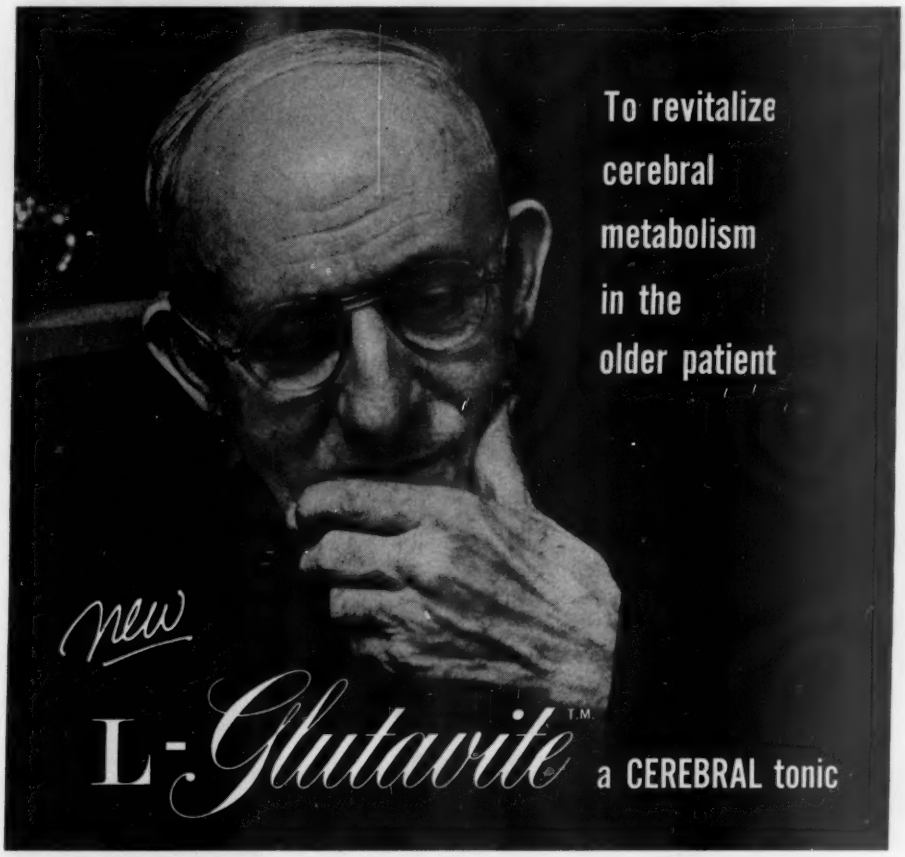

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1. Himwich H.E.: Paper presented at American Psychiatric Association meeting, St. Louis, May, 1954.
2. Lehmann, H.: 27th Annual Conference, Milbank Memorial Fund, New York, Paul B. Hoeber, Inc., 1952. p. 587.

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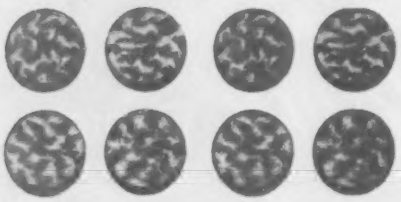

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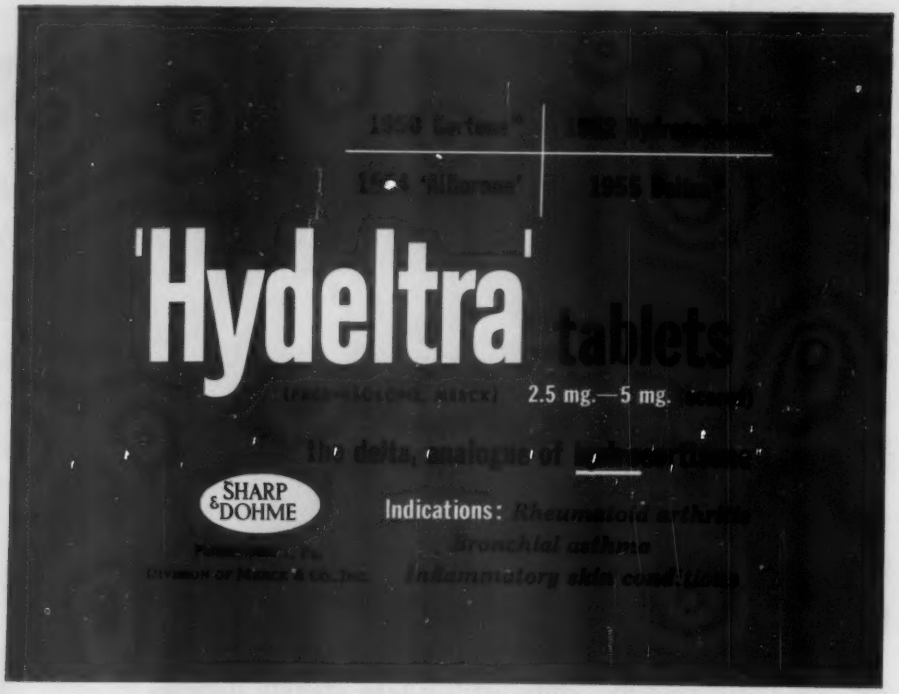

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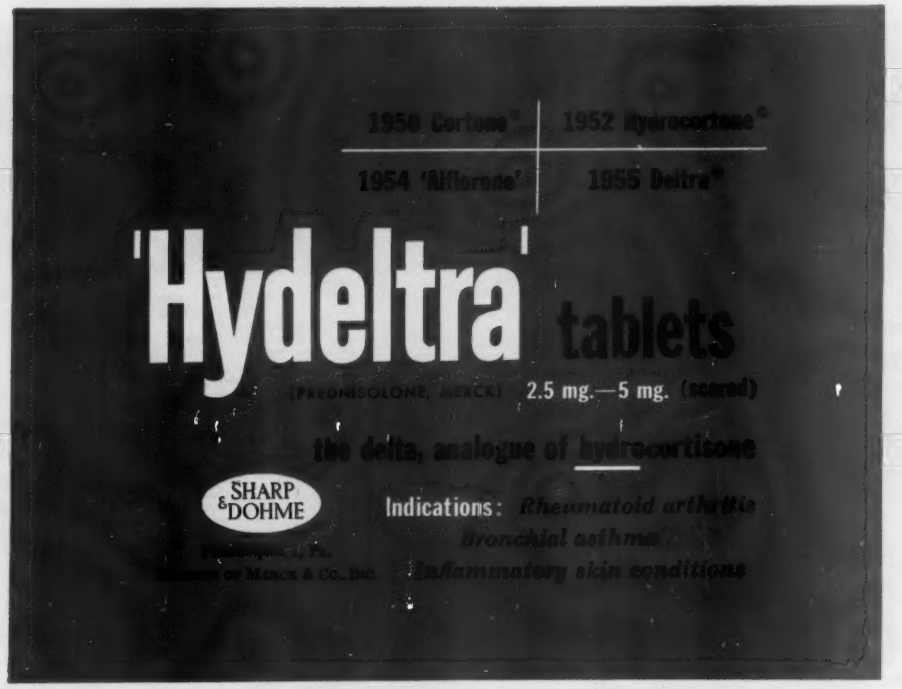

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10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

SATURDAY, SEPTEMBER 17
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

MONDAY, SEPTEMBER 19
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.

TUESDAY, SEPTEMBER 20
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
12:00 m. South End Medical Club. Boston Tuberculosis Association, 554 Columbus Avenue, Boston.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, SEPTEMBER 21
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*11.00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
6:45 p.m. Essex North District Medical Society. Haverhill Country Club, Haverhill.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

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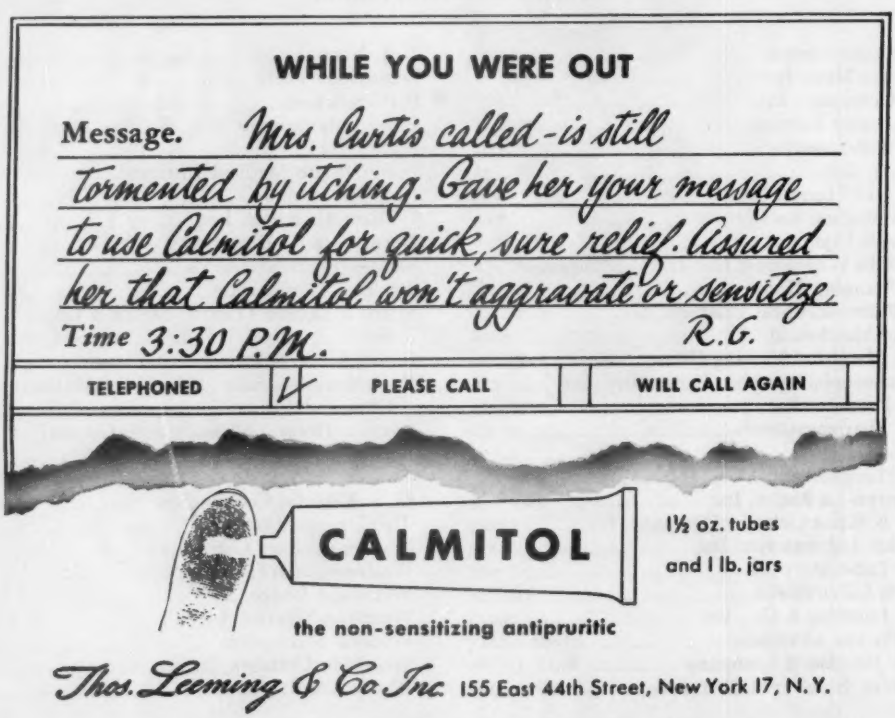
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1. Rosenberg, S. and Oster, K. A., "Gelatine in the Treatment of Brittle Nails," *Conn. State Med. J.* 19:171-179, March 1955.
2. Tyson, T. L., *J. Invest. Dermat.* 14:323, May 1950.

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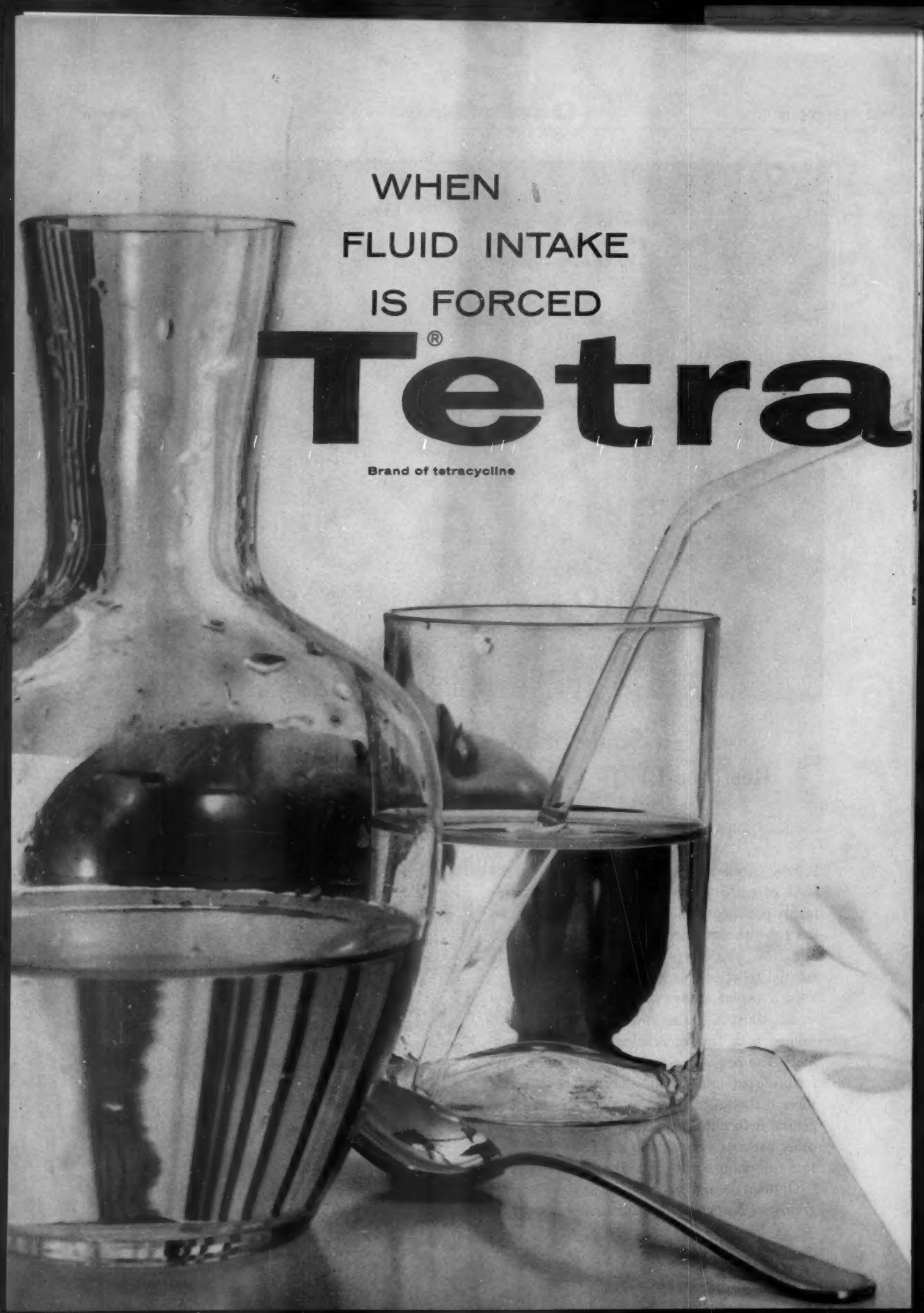
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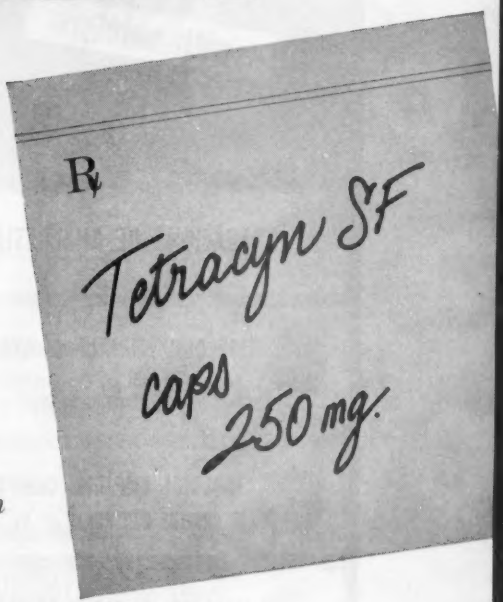

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